The Patient Generated Index (PGI) as an early-warning system for predicting brain health challenges:

A prospective cohort study for people living with Human Immunodeficiency Virus (HIV)

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LIST OF ABBREVIATIONS

+BHN	Positive Brain Health Now
AI	Artificial intelligence
ANI	Asymptomatic neurocognitive impairment
ART	Antiretroviral therapy
AS	Ankylosing Spondylitis
AUROC	Area-under-the-receiver-operating-characteristic curve
BAI	Beck Anxiety Inventory
B-CAM	Brief Cognitive Ability Measure
BDI	Beck Depression Inventory
BERT	Bidirectional Encoder Representations from Transformers
C3Q	Communicating cognitive concerns questionnaire
CAHR	Canadian Conference on HIV/AIDS Research
CaRT	Classification and regression tree
CBT	Cognitive Behavioural Therapy
CES-D	Center for Epidemiologic Studies Depression Scale
CHIWOS	Canadian HIV Women's Sexual and Reproductive Health Cohort Study
CI	Confidence intervals
ClinROs	Clinically reported outcomes
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
EQ-5D	European Quality of Life-5 Dimensions
EQ-5D-5L	EuroQoL 5 Dimension 5 Level
GAD	Generalized anxiety disorder
GDS	Geriatric Depression Scale
GEE	Generalized estimating equations
GHQ	General Health Questionnaire

GPS	Graduate and Postdoctoral Studies
HAD	HIV-associated dementia
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS subscale for anxiety
HADS-D	HADS subscale for depression
HAM-D	Hamilton Depression Rating Scale
HAND	HIV-associated neurocognitive disorder
HIV	Human Immunodeficiency Virus
HRQOL	Health related quality of life
HUI®	Health Utilities Index
ICC	Intraclass correlation coefficient
ICD	International Classification of Diseases
ICF	International Classification of Functioning, Disability and Health
LGBTI	Lesbian, gay, bisexual, trans, and intersex
MADRS	Montgomery-Asberg Depression Rating Scale
MHI	Mental Health Index
MLP	Multi-layer perception
MND	Mild neurocognitive disorder
MOS-HIV	Medical Outcomes Study-HIV Health Survey
MQOL-HIV	Multidimensional Quality of Life Questionnaire for Persons with HIV/AIDS
MS	Multiple Sclerosis
NLP	Natural language processing
OR	Odds ratios
PDQ	Perceived Deficit Questionnaire
PerfOs	Performance outcomes
PFI	Physical Function Index
PGI	Patient Generated Index
PHQ	Patient Health Questionnaire

PHQ-9	Patient Health Questionnaire depression module
PROs	Patient-reported outcomes
PROMs	Patient-reported outcome measures
PRO MDD	Patient-reported outcome for major depressive disorder
PROMIS	Patient-Reported Outcomes Measurement Information System
PTSD	Post-traumatic stress disorder
QALYs	Quality-adjusted life-years
QOL	Quality of life
RF	Random Forest
SD	Standard deviation
SDS	Zung Self-rating Depression Scale
SF-36	36-Item Short Form Health Survey
SF-6D	Medical Outcomes Study Short-Form 6 Dimensions
SFA	Self-focused attention
SMDDS	Symptoms of Major Depressive Disorder Scale
SROs	Self-reported outcomes
STAI	State Trait Anxiety Index
SVM	Support Vector Machine
TechOs	Technology assessed outcomes
UNAIDS	The Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization
WHOQOL-HIV-BREF	World Health Organization's Quality of Life Instrument in HIV Infection

ABSTRACT

By the end of 2020, there were an estimated 37.7 million people living with Human Immunodeficiency Virus (HIV) across the globe with about 65,811 in Canada. While there is no cure, HIV infection has become a manageable chronic health condition. As a result, there is now a substantial population of people aging with HIV. Aging with HIV has important consequences for brain health arising from neurobiological factors associated with the illness and its antiretroviral therapy (ART) as well as from psychosocial factors related to social stigma and social interaction.

The most impactful brain health concerns are psychological distress, depression, anxiety, and cognitive impairment. These concerns are often queried in clinical encounters but rarely using standardized methods. In research, standardized questionnaires are used with items querying serious health concerns. Typically, these concerns are not identified until the statistician analyses the data. An alternative for both clinical and research purposes is to use an individualized measure where people are asked to self-nominate areas of concern which can then be dealt with in real-time. These areas reflect sentiments which could be used to identify people with brain health challenges who need further investigation. The relevance of this approach to identify brain health concerns has not been explored in people aging with HIV.

The primary objective of this thesis was to estimate the extent to which a self-nomination of areas related to mood and cognition on an individualized measure, the Patient Generated Index (PGI) predicts the presence or emergence of psychological distress, depression, anxiety, or cognitive impairment among people with HIV at the first assessment at study entry and for successive assessments over 27-months.

The data comes from participants enrolled in the Positive Brain Health Now (+BHN) cohort (n=856). The nominated areas were category coded to a sentiment framework. Logistic regression was used to link self-nominated sentiments to presence or emergence of psychological distress, depression, anxiety, or low cognitive ability as assessed using standardized measures of these constructs. Analyses yielded odds ratios (OR), their 95% confidence intervals (CI) and c-statistics indicating prediction accuracy.

Decision trees have been utilized along with other models associated with emotion detection. A classification and regression tree (CaRT) model was applied to identify the most relevant and independent sentiments that contributed to each brain health concern. A standardized difference of 10% was used to identify the pathways associated with people having a greater prevalence of the threshold value.

Emotional sentiments predicted all of the brain health outcomes at all visits with adjusted ORs ranging from 1.61 to 2.00 and c-statistics >0.73 (good to excellent prediction). Nominating an anxiety sentiment was specific to predicting anxiety and psychological distress (OR: 1.65 & 1.52); nominating a cognitive concern was specific to predicting self-reported cognitive concerns (OR: 4.78). Positive sentiments were predictive of good cognitive function (OR: 0.36) (Manuscript 1 submitted).

The CaRT model showed two pathways each for psychological distress, clinically important depression, clinically important generalized anxiety and three pathways that led to cognitive difficulties. Cognitive sentiments were the most discriminatory for cognitive difficulties. The prevalence of low cognitive ability for people nominating cognitive sentiments was 50.7%, and for people classified as not working (with <15 hours/week of paid employment), nominating additional emotional sentiments, resulted in a prevalence rate of 82.4%. Emotional sentiments were the most discriminatory for both psychological distress and clinically important generalized anxiety. Positive sentiments were protective of good cognitive function and depressive symptoms (Manuscript 2 submitted).

This study indicates the value of using a semi-qualitative approach as an early-warning system for predicting the presence or emergence of brain health challenges from the spontaneously nominated life areas within the PGI.

ABRÉGÉ

À la fin de 2020, on estimait à 37,7 millions le nombre de personnes vivant avec le virus de l'immunodéficience humaine (VIH) dans le monde, dont environ 65 811 au Canada. Bien qu'il n'y ait pas de remède, l'infection au VIH est devenue un problème de santé chronique gérable. Par conséquent, il y a maintenant une population importante de personnes qui vieillissent avec le VIH. Le vieillissement avec le VIH à d'importantes conséquences sur la santé du cerveau qui découlent de facteurs neurobiologiques associés à la maladie et à son traitement, antirétroviral (TAR) ainsi que de facteurs psychosociaux liés à la stigmatisation sociale et à l'interaction sociale.

Les problèmes de santé cérébrale les plus importants sont la détresse psychologique, la dépression, l'anxiété et les troubles cognitifs. Ces préoccupations sont souvent soulevées lors de rencontres cliniques, mais rarement à l'aide de méthodes standardisées. En recherche, des questionnaires standardisées sont utilisés avec des articles interrogeant des problèmes de santé graves. En règle générale, ces préoccupations ne sont pas détectées tant que le statisticien n'a pas analysé les données. Une solution de rechange à des fins cliniques et de recherche consiste à utiliser une mesure individualisée où on demande aux gens de désigner par eux-mêmes les sujets de préoccupation qui peuvent ensuite être pris en charge en temps réel. Ces domaines reflètent des sentiments qui pourraient être utilisés pour identifier les personnes ayant des problèmes de santé cérébrale qui ont besoin d'une enquête plus approfondie. La pertinence de cette approche pour cerner les problèmes de santé du cerveau n'a pas été explorée chez les personnes qui vieillissent avec le VIH.

L'objectif principal de cette thèse était d'estimer dans quelle mesure l'identification par le participant des facteurs liés à l'humeur et à la cognition basée sur une mesure individualisée, Patient Generated Index (PGI), prédit la présence ou l'émergence de détresse psychologique, de dépression, d'anxiété ou de troubles cognitifs, chez les personnes vivant avec le VIH, lors de la première évaluation de cette étude et lors des évaluations suivantes, sur une période de 27 mois.

Les données proviennent de participants inscrits à la cohorte Positive Brain Health Now (+BHN) (n=856). Les domaines identifiés ont été classés selon un cadre de sentiment. Une régression logistique a été utilisée pour établir un lien entre les sentiments identifiés par les participants et la

présence ou l'émergence de détresse psychologique, de dépression, d'anxiété ou de faible capacité cognitif, selon les mesures normalisées de ces concepts. Les analyses ont produit des rapports de cotes (RC), leurs intervalles de confiance (IC) à 95 % et des statistiques c indiquant l'exactitude des prévisions.

Des arbres de décision ont été utilisés avec d'autres modèles associés à la détection des émotions. Un modèle d'arbre de classification et de régression (CaRT) a été appliqué pour identifier les sentiments les plus pertinents et indépendants qui ont contribué à chaque problème de santé du cerveau. Une différence normalisée de 10 % a été utilisée pour déterminer les embranchements associés aux personnes ayant une prévalence plus élevée de la valeur seuil.

Les sentiments émotionnels prédisaient tous les résultats pour la santé du cerveau à toutes les visites avec des rapports de cotes ajustés (RC) allant de 1,61 à 2,00 et des statistiques c >0,73 (prédiction bonne à excellente). L'identification d'un sentiment d'anxiété était propre à la prédiction de l'anxiété et de la détresse psychologique (RC : 1,65 et 1,52); l'identification d'une préoccupation cognitive était propre à la prédiction de préoccupations cognitives autodéclarées (RC : 4,78). Les sentiments positifs étaient prédictifs d'une bonne fonction cognitive (RC : 0,36) (manuscrit 1 soumis).

Le modèle CaRT a montré deux embranchements chacun pour la détresse psychologique, la dépression cliniquement importante, l'anxiété généralisée cliniquement importante et trois voies qui ont conduit à des difficultés cognitives. Les sentiments cognitifs les plus discriminatoires étaient les difficultés cognitives. La prévalence d'une faible capacité cognitive chez les personnes qui nommaient des sentiments cognitifs était de 50,7 %, et chez les personnes classées comme ne travaillant pas (avec moins de 15 heures/semaine d'emploi rémunéré), qui nommaient des sentiments émotionnels supplémentaires, a donné un taux de prévalence de 82,4 %. Les sentiments émotionnels les plus discriminatoires étaient la détresse psychologique et l'anxiété généralisée cliniquement importante. Les sentiments positifs protégeaient une bonne fonction cognitive et des symptômes dépressifs (manuscrit 2 soumis).

Cette étude indique l'intérêt d'utiliser une approche semi-qualitative comme système d'alerte précoce pour prédire la présence ou l'émergence de problèmes de santé du cerveau à partir des sujets de préoccupation spontanément désignés à l'aide du l'PGI.

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I would express gratitude to my supervisor Dr. Mayo for accepting me as her student and for her continuous support throughout my studies. Dr. Mayo provided me with the direction that I needed to reach my research objectives. Her patience, extensive knowledge, and the ability to constantly adapt to the needs of the project is priceless. This thesis would not have been possible without her thoughtful supervision and continuous guidance.

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PREFACE

Contribution of authors

This thesis is a part of the longitudinal cohort study entitled, "Understanding and optimizing brain health in HIV now" conceived by Dr. Lesley Fellows, Dr. Marie-Josée Brouillette and Professor Nancy Mayo. The data arising from the Positive Brain Health Now (+BHN) cohort were used for the analyses.

The manuscripts included in this thesis are the work of Muhammad Mustafa Humayun with editing and feedback from Dr. Mayo and support from all of the members of the thesis supervisory committee. Both manuscripts were written by the master's candidate. For manuscript 1, statistical analysis was conducted by the candidate. As supervisor, Dr. Mayo oversaw all aspects of the thesis and provided expertise regarding research methodology and statistical analyses.

Dr. Brouillette and Dr. Fellows were the primary investigators of the +BHN study and provided professional feedback for each manuscript.

M. Mehmet Inceer, a doctoral candidate associated with the +BHN cohort, helped with the regression tree approach and presentation of the results in Manuscript 2. The candidate completed the pruning of the tree models, prepared the pathway tables, and wrote the manuscript.

Thesis organization and overview

The thesis consists of two manuscripts which are being prepared for submission and review by recognized scientific journals. An abstract for the first manuscript titled, "The patient generated index (PGI) as an early-warning system for predicting brain health challenges: a prospective cohort study for people living with Human Immunodeficiency Virus (HIV)" was recently accepted for a poster presentation at the 31st Annual Canadian Conference on HIV/AIDS Research (CAHR 2022), held on April 27-29, 2022. The abstract has been accepted for a poster presentation at the 13th International Workshop on HIV & Aging that will be held on 13-14, October 2022 in Boston. Manuscript 1 is being finalized for submission to Nature Mental Health.

To comply with the requirements of the Graduate and Postdoctoral Studies (GPS), additional chapters and sections have been included in this thesis which show a natural progression and the initial research work required to prepare the manuscripts. As required by the GPS, introductory and concluding sections independent of the manuscripts have been incorporated into the thesis. McGill University guidelines for manuscript-based thesis were followed which recognize the manuscripts as concise documents.

This thesis consists of five objectives presented in sequence within the chapters and the associated manuscripts. The first objective is to provide an overview of the brain health concerns and measures; this serves as an introduction. The second objective is to introduce the PGI and the domains identified on the measure across different chronic concerns. The third objective is to conduct a review of the sentiment analysis literature regarding brain health concerns to identify the high-risk sentiments associated with depression, anxiety, and cognitive impairment. The fourth objective is to estimate the extent to which self-nomination of areas related to mood, anxiety, and cognition sentiments on the PGI predict the presence or emergence of specific brain health concerns among people with HIV at study entry and for successive assessments over 27-months. The fifth objective is to estimate the extent to which a self-nomination of areas related to mood, anxiety, and cognition sentiments on the PGI are associated with a greater prevalence of brain health concerns among people with HIV.

A brief outline of the thesis is as follows:

Chapter 1 provides a synopsis of the brain health concerns, standard outcome measures and an overview of the participants to be covered by this thesis. Early on, the introductory section discusses the changing demographics of an aging population of people with HIV. The components of brain health, brain health concerns and the associated symptoms are then identified before comparing self-report and performance-based measures.

Chapter 2 reviews the psychometric properties of the PGI, identifies its association with brain health outcomes, conducts a review of the domains nominated on the measure and compares these with the standard outcome measures of brain health.

Chapter 3 presents a review of the sentiment analysis literature related to brain health outcomes and the high-risk sentiments associated with depression, anxiety, and cognitive impairment.

Chapter 4 provides the overall objective and rationale behind the research.

Chapter 5 consists of the first manuscript entitled, "The PGI as an early-warning system for predicting brain health challenges: a prospective cohort study for people living with HIV." The objective of this manuscript is to estimate the extent to which a self-nomination of areas related to mood, anxiety, or cognition on the PGI predict the presence or emergence of psychological distress, depression, anxiety, or cognitive impairment among people with HIV at study entry and/or at successive assessments over 27-months.

Chapter 6 consists of the second manuscript entitled, "The PGI as an early-warning system for predicting brain health challenges: tree analysis modeling of sentiments." The objective of this manuscript is to estimate for a cohort of middle-aged and older people with HIV the extent to which a self-nomination of areas related to mood, anxiety, and cognition on the PGI are associated with a greater prevalence of brain health concerns including psychological distress, depression, anxiety and cognitive difficulties.

Chapter 7 provides an integration and the summary of the findings of the two manuscripts.

Chapter 8 provides a discussion and a conclusion to the thesis while considering the findings, lessons learned and the next steps in this area of research.

Tables, figures, and references are presented at the end of each manuscript. Also, the appendices include information that was important to include in the thesis but not necessarily presented in the manuscripts.

CHAPTER 1: An overview of brain health concerns and measures

1.1-Introduction

By the end of 2020, there were an estimated total of 37.7 million people with Human Immunodeficiency Virus (HIV) (1) with about 65,811 in Canada (2-4). In 2020, HIV-related causes claimed an estimated 680,000 lives across the globe(1). About 73% of people with HIV in high-income countries are estimated to be over 50 years by 2030 (5).

While there is no cure, the HIV infection has become a manageable chronic health condition. Effective antiretroviral therapies (ART) have greatly improved the life expectancy of people living with HIV. It is a complex chronic condition affecting an aging population that often faces multiple psychosocial disadvantages, including economic vulnerability, stigmatization, and discrimination. As a result, there is now a substantial population of people aging with HIV.

People with HIV are also at greater risk of several comorbidities and psycho-behavioural challenges. Although treatments to manage brain health concerns are available, depression continues to be a leading cause of disability in people with HIV (6). More recently, the prevalence of depression in people with HIV was estimated to be 39% (7). The prevalence of depression in the aging (>50 years) segment of the population is estimated to be over 50% (8). Depression is under-diagnosed in the aging population due to the difficulty in distinguishing the somatic symptoms of depression and ART (9).

The Joint United Nations Programme on HIV/AIDS (UNAIDS) targets for global HIV control called for reaching the 90% target for diagnosis, ART, and viral suppression of HIV also referred to as its 90-90-90 targets for 2020 (10). Advocates called for a need to ensure that 90% of the people with viral load suppression have a good health related quality of life (HRQOL) (10, 11). Despite the ART efficacy, the viral undetectability, people with HIV report a decreased HRQOL compared with the general population (12-14). There is a growing agreement among the proponents of the fourth 90 that a simultaneous assessment of these constructs can enable the testing and identification of the associations between wellbeing (both mental and physical) and related variables (15). More recently, new fast-track targets were set at 95-95-95 to be achieved by 2030 (16). UNAIDS acknowledged the fourth 90/95 by probing mental wellness in its new lesbian, gay, bisexual, trans, and intersex (LGBTI) survey for HIV. This 82-question online survey asked about family support, sexual satisfaction, physical health, happiness, self-esteem, outness, and internalized homophobia (10).

About 10.7% of the global population lives with a mental health disorder (17). In Canada, the economic burden of mental health concerns in terms of a loss of productivity and medical costs is estimated to be in the range of $14.4-$51 billion (18-20). A nationally representative sample in the United States estimated the 12-month prevalence of mood (9.5%), anxiety (18.1%) and for any disorder (26.2%) (21). Higher rates of mental health disorders have been observed in people with HIV (38.6%) when compared with the general population (22-25). The prevalence ratio of current major depression in people with HIV receiving care and the general population was estimated to be 3.1 in the United States (24). People with chronic concerns tend to have a shortened lifespan when they experience comorbidities such as severe mental, neurological or, substance use disorders (26). Service disruptions during the COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), slowing public health response to HIV, and a growing mental health burden on this aging population presents challenges that need to be tackled (27-29).

Aging with HIV has important consequences for brain health arising from neurobiological factors associated with the illness and the ART as well as from psychosocial factors related to social stigma, and social interaction (30-35). Brain health concerns including depression, anxiety and cognitive difficulties are associated with ART adherence, therapeutic effect, quality of life (QOL) and physical function in people with HIV (33, 36-43).

1.2-Brain health and its components

There is no universally accepted definition of brain health while most definitions tend to focus on the general functioning of the brain or emphasize on a narrow range of dimensions associated with brain health. Early neurological definitions focused on the absence of disease while more recent definitions consider the state of complete physical, mental and social wellbeing of the brain (44).

The World Health Organization (WHO) defines good brain health, "as a state in which every individual can realize their own abilities and optimize their cognitive, emotional, psychological and behavioural functioning to cope with life situations (45)." The brain is associated with the maintenance of cognitive, mental and emotional processes, normal behaviour and social cognition

(46). Thus, the definition of brain health includes the optimal preservation of both mental and cognitive functions (46). My research focuses on predicting brain health concerns including psychological distress, depression, anxiety, and cognitive ability. Also, physical, social, somatic, and other aspects related to brain health are considered for predicting brain health outcomes.

1.3-Brain health concerns and the associated symptoms

1.3.1-Mood and depressive symptoms

Mood is defined as a blend of emotions felt by a person over the passage of time and is representative of the general emotional state of a person's perception of the world (47). Fluctuations in intensity, duration and the instability of mood is often a feature of brain health concerns of anxiety and depression (48). Moods can be characterized as depressed, irritable, expansive, euthymic, and more (47-49). Emotions are short-lived affective states such as happiness, anger, disgust, fear and so on; these may have a somatic component and can be caused by physiological changes in response to an event (47). Changes in mood can alter a person's energy and behaviour including physical mechanisms such as pain, hunger, satiety, muscle tension and sexual satisfaction (47). Mood disorders may lead to emotional inflexibility and normal emotions can often last for much longer than circumstances permit (50). Since perception and thoughts are best retained when connected to strong emotional memories, mood is also associated with cognition (51-53). This can lead to selective recall, memory distortion and change the perception of self-worth which is a component of the experiences, abilities, and future plans of a person (51, 53).

Mood disorders can be disruptive to the patients' QOL due to their recurrent nature and tend to be relatively common. In Canada, it is estimated that only half of the people with the symptoms associated with mood disorders are professionally diagnosed (54). Other studies corroborate that about 20% of the primary care patients are clinically depressed but approximately half of these patients tend to be diagnosed by a physician (55, 56). Underdiagnosis of mood disorders may be associated with the presentation of unexplained somatic symptoms including pain and insomnia in chronic conditions (47). Mood disorders are not associated with "will power" or motivation, instead these are medical illnesses that require active detection and diagnosis by a clinician (47, 57). The duration, intensity and the extent of functional impairment in a mood disorder is clearly distinguished from natural variations in mood and suitable reactions to stress (47).

An episode of major depression presents in terms of a persistent and distinct feeling of loss of pleasure or interest (58). Depressed mood is often associated with feelings of sadness, emptiness, the need to cry, and emotional states of anxiety, irritability and/or hostility (59, 60). Sadness is often accompanied with lowered self-esteem, self-criticism, inadequacy, or a sense of guilt (59, 61, 62). A disproportionate response to an event is indicative of depression and not merely the presence of depressive symptoms (63). Thus, a normal response to events such as the death of a loved one, experiencing a significant financial loss, or retirement may result in depressive symptoms and still not merit a clinical diagnosis of depression (64, 65). Whereas extended periods of depressed mood for at least 2 weeks, or an increasing intensity of depressive symptoms may signal a higher probability of the presence of depression or a mood disorder (66, 67).

For aging people with HIV in Canada, mental health experiences included stories related to resilience, stigma and uncertainty (68). In-depth interviews revealed experiences of medical uncertainty, discrimination in healthcare interactions, and feeling stigmatized due to physical appearance (68). Worries related to housing and related expenses were an important other contributor to depression (69). Neuropsychiatric symptoms formed 61% of the comorbidities (70). Central themes emerging from the lived experience of aging people with HIV in Quebec included premature aging, impact on intergenerational relationships, dwindling social networks, rejection due to age, difficulty returning to work and worsening living conditions (71). Depression (32.3%) and anxiety (29.5%) were the most prevalent comorbidities reported for the Canadian HIV Women's Sexual and Reproductive Health Cohort Study (CHIWOS) (72). The mental HRQOL score was 41.7 when compared with 50.9 for the general female population (73). A lower physical health score was closely associated with an increase in stress and depressive symptoms in this aging population (73). Adult women with HIV (aged $\geq$ 40) in another Ontario-based cohort were higher on the spectrum of increasing severity of depressive symptoms when compared with adult men living with HIV (74).

For people with HIV, it can be particularly difficult to differentiate between the somatic symptoms associated with chronic illness and the depressive state (75). Side effects from the ART such as the psychiatric disturbances or weight gain can mirror depressive symptoms (76). A lack of full adherence to ART may be associated with some of the symptoms of depression. A pooled sample (n=7,375) found that adherence to ART was 52% and depressed people with HIV were less likely to adhere to ART when compared with those who were not depressed (77). The relationship between depression and ART remains inconclusive (77). In a Canadian sample (n=57), self-assessment of depression and adherence to ART showed moderate adherence rates (66.7% were ≥ 95% adherent) for people with HIV born outside Canada and (51.6% were ≥ 95% adherent) for those born in Canada(78). For those born in Canada, symptoms of depression were associated with lower ART adherence in this sample (78).

The somatic-vegetative symptoms such as a change in appetite, fatigue, reduced energy, sleep disturbance and weight gain are also common in people with HIV, especially when there is low adherence to ART and in the aging population. The cognitive-affective symptoms include diminished concentration, low self-worth, and psychomotor retardation (79, 80). Cognitive-affective symptoms of depression which are the secondary symptoms may be more reliable in chronic conditions like HIV (80-82).

1.3.2-Symptoms of anxiety and anxiety disorders

Anxiety is a normal human emotion associated with behavioural, physiological, and psychological factors. Moderate or low levels of anxiety can be highly adaptive and act as a motivator for improved performance and increased attentiveness (47). Anxiety can become maladaptive if it occurs in the absence of a stressor or when its intensity is disproportionate to the level of threat (83, 84). The disorders associated with anxiety are often ineffective adaptations to normal or naturally occurring threats such as diseases, environmental hazards, and social conflicts (47, 85). These symptoms can range from psychological to somatic while distress is often restricted to worry or concern about such experiences and symptoms (47). The psychological distress associated with anxiety can lead to physical symptoms such as shortness of breath, palpitations, sweating or diarrhea while avoiding the stressors may result in a lack of adaptation to the stressor (47).

Anxiety is clinically recognized as a disorder when its persistence impairs the functioning of a person in social, familial, and work-related situations (86, 87). The clinical diagnosis of anxiety may include generalized anxiety disorder (GAD), panic disorders, post-traumatic stress disorder (PTSD) and phobic disorders (83). It is important to distinguish between clinical diagnosis of mental health concerns including depression and anxiety with the prevalence of the symptoms associated with these concerns as identified using self-report questionnaires.

People with HIV experience several recurrent stressors that can lead to the symptoms associated with anxiety such as physical pain, side-effects of ART, social stigma, discrimination and more

(88). The prevalence rate of anxiety in people with HIV is estimated to be as high as 38% compared to about 11 percent in the general population (89-91). Anxiety symptoms and disorders are the most common class of psychiatric disorders in people with HIV; however, there is much less research focus on this area when compared to the study of depressed mood and psychopathology (88).

1.3.3-Cognitive impairment in people living with HIV

In people with HIV, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD) are determined to be distinct categories for clinical diagnosis of HIV-associated neurocognitive disorders (HAND) (92, 93). A decline in cognitive functioning is the defining feature of the illness for patients experiencing neurocognitive disorders (94). Clinical diagnosis is critical to prevention, treatment, and management of a specific concern.

Cognitive ability is an increasingly important consideration in aging populations including people with HIV. MND is recognized as a degree of cognitive ability between normal aging and dementia (95). Population-based studies estimate the prevalence of MND for people aged 60 or more to be between 15% to 20% (47, 95). Studies show that annually between 8% to 15% of the people with MND in the general population progress to dementia (95). Cognitive concerns may present as cognitive decline, or in terms of lower cognitive ability that is not normal for a specific age group (95). Also, cognitive concerns may include memory impairment or the impairment of a single non-memory cognitive domain (95). MND presents as modest but clear cognitive decline outside of normal aging. The domains used to assess major neurocognitive disorders are also relevant for the assessment of MND (47). Thus, early detection of cognitive concerns can facilitate reaching an appropriate diagnosis, treatment plan, and counseling of people with specific concerns including people aging with HIV who are at risk of impairment and dementia.

Initial symptoms of cognitive decline in aging populations may include forgetting names, becoming confused about directions and/or neglecting to turn off the lights while the long-term memory persists until late stage neurocognitive decline (47). People with cognitive decline may seem apathetic, depressed or dull and may present fluctuating moods (47). Thus, it is important for the clinician to distinguish between pseudo-dementia, pseudo-depression and neurocognitive decline (96). Pseudo-dementia is a psychiatric condition not related to neurocognitive decline and is reversible through successful treatment or resolution of the psychiatric condition to a large extent (96, 97). Pseudo-depression is often associated with apathy which is related to a lack of motivation in combination with behavioural and affective changes while depression is associated with mood affects and is not related to apathy (96).

1.4-Defining outcomes and measures of brain health

Different sources provide information on brain health outcomes including the patient, the family, the clinician, and certain tests and images. Several types of measures are used to assess the symptoms and signs associated with psychological distress, depression, anxiety, and cognitive ability. Some such measures are diagnostic or identify those who may need to be referred for further evaluation and some measure these outcomes as quantities.

1.4.1-Types of sources of information and measures on brain health outcomes

1.4.1.1-Types of sources

In the work by Mayo and colleagues (98), there are multiple sources of information about brain health outcomes. One source is the patient or person themselves. When they report on outcomes for which only their experience is valid and their rating cannot be interpreted or altered by another person, these are called patient-reported outcomes (PROs) and the measures of these outcomes are termed PROMs. PROMs are used to acquire data on symptoms, such as pain, fatigue, or emotions, perceptions such as about health or QOL, difficulty or confidence with activities, and satisfaction with experiences. Patient reported outcome measures (PROMs) were generally acceptable and easy to use by people with Human Immunodeficiency Virus (HIV) with lower acceptability associated with illicit opioid use, multiple recent sex partners and higher symptoms of depression (99).The patient or person can also self-report via self-reported outcomes (SROs) on limitations in function, such as physical or cognitive limitations, but these reports could be verified by another if needed for purposes of safety or resource allocation.

Clinically reported outcomes (ClinROs) refer to the appraisals completed by trained professionals and may involve clinical judgment or interpretation of observable indications, behaviours or physical signs (98). Some measures have clinicians rate what a patient says rather than having the patient do it themselves and these are best called clinician-rated measures.

Some outcomes require expert examination or technology for measurement while other constructs can be accurately reported by people or patients (98). Performance outcomes (PerfOs) include tests of walking, dexterity and cognition which require patient cooperation and motivation (98). A PerfO is a measurement based on a task or a number of tasks performed according to the instructions provided and administered by a healthcare professional (98). Likewise, technology assessed outcomes (TechOs) include pulmonary and cardiac function tests, neuroimaging for neurological conditions, physical activity, medication adherence and community mobility (98). PerfO and TechO measures have calibrated units.

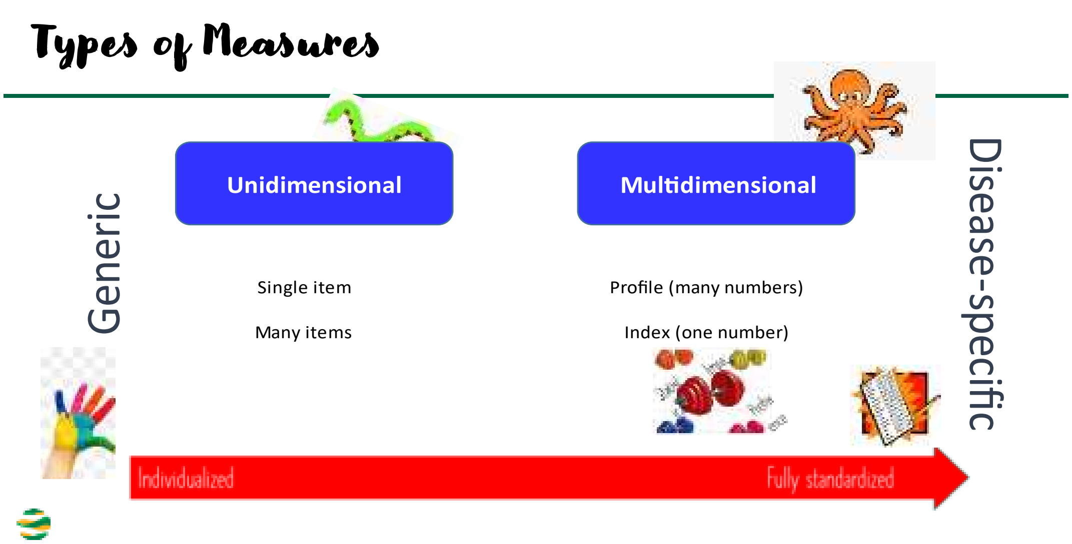
SROs are not the same as PROs because the interpretation of what a patient reports they can do may be altered based on other evidence that may not be provided directly by the patient (98). It is prudent to validate self-reports using other sources of information especially when the outcomes are used to ascertain level of care or safety (98).

Information on brain health outcomes can be gathered from all of these sources, although it is most common to use PROMs for symptoms, SROs and PerfOs for cognitive ability, and TechOs for brain structure and function (not the topic of this thesis).

1.4.1.2-Types of measures

Figure 1 (taken from the teaching notes of Prof. Mayo) outlines the types of PROMs or SRO measures that are available for assessing brain health outcomes.

Figure 1: Types of measures



Measures can be generic or disease specific. Generic measures can be used for people with different health conditions or in the general population. Examples of generic measures used to assess some aspects of brain health include the PROMs, 36-Item Short Form Health Survey (SF-36), European Quality of Life-5 Dimensions (EQ-5D), and the Hospital Anxiety and Depression Scale (HADS) (100). Although, generic measures provide useful information and enable a comparison with the general population, the content may not reflect the unique aspects related to HIV such as fear of disclosure, stigma, or discrimination. Disease or condition-specific measures are designed to be used in specific populations. These condition-specific measures allow a better understanding of the relative health related impact and have shown an improvement in the discriminant validity and responsiveness when compared with generic measures (101). These condition-specific measures or questionnaires ask specific questions relating to a health condition. An example of a disease specific measure in HIV is the Medical Outcomes Study-HIV Health Survey (MOS-HIV) which was adapted from the SF-36 (102). Disease or condition-specific measures are developed specifically for people with a health condition and cover content that pertains to each condition.

These generic or disease-specific measures can be of single constructs or domains, termed unidimensional, such as measures of symptoms or physical function. These can be measured using one item only (103) or multiple items (104, 105). Measures can also be multi-dimensional of the profile type (one value for each dimension) or indices where there is one value for all of these dimensions.

PROs need to incorporate patient input and as patients are a more diverse group, these measures are often developed more rigorously in comparison with ClinROs (98). Clinicians are often reluctant to rely on patient's reports of change in their health condition since response shift can lead to a change in the patient perspectives of their health that is not related to change in the target construct (98). From the patient's perspective, the concept of health refers to how healthy one feels while from the clinician's perspective health refers to the physiological abnormalities that are detectible in a person's body (98, 106). It is recognized that both the patient and clinician perspectives are important when assessing health and QOL. Thus, sensitivity to clinical change or responsiveness is an important consideration when selecting a PRO for clinical and research applications (107).

Measures can also be fully standardized or individualized. Standardized outcome measures are the basis for evidence-based practice (108, 109); everyone responds to the same questions whether they are relevant or concerning to them or not. Individualized outcome measures acknowledge that there is variation in how people see the impact of a health condition and this affects treatment approaches (110). In rehabilitation studies, responsiveness to intervention has been reported higher for individualized measures when compared with traditional fully standardized measures (110).

One individualized measure is the Patient Generated Index (PGI) which will be discussed in detail in the next chapter.

1.4.1.3-Scoring

PROs and SROs usually have ordinal rating scales that are summed to yield a quasi-continuous measurement scale. There are a number of limitations to this approach and now it is essential that this practice is validated using modern measurement approaches (111, 112). Another form of scoring for these measures is to use preference weights, how much a person values that area in comparison to other areas. Preference-based outcome measures are often used to inform decisions about healthcare resource allocation and to estimate quality-adjusted life-years (QALYs) (113, 114).

Such measures are comprised of a descriptive set of domains that are used by the patients to describe aspects of their health such as pain and discomfort or limitations in daily activities (115). The areas in the descriptive system are valued by the general population in a specific area or country (114, 116, 117) and then converted to an index score. The scores ranging from 0 to 1, where 0 refers to “death” and 1 is indicative of “full health” (118). Values below zero may be possible in some contexts as there are health states worse than death (119). The EQ-5D, Medical Outcomes Study Short-Form 6 Dimensions (SF-6D) and Health Utilities Index (HUI®) are examples of preference-based measures (115). These generic measures can be used across health conditions and in the general population. The EQ-5D is the most widely used generic preference-based measure of HRQOL with index scores ranging between 0 and 1 (120). There is currently no HIV-specific preference-based measure of HRQOL although one is under development by the research team supervising my research program.

1.4.2-Measurment approaches to depression symptoms

Several outcome measures can be used to assess the prevalence of depression in the general adult population, children and the elderly (100). The measures differ in terms of the concepts covered, diagnostic usefulness, length, recall period, response options and scoring (100, 121, 122). More often than not, such measures are not specific to the unique contexts of clinical populations such the people with HIV including the psychological implications associated with the condition and the need to address the constructs of age, culture, sex and race (123). These unique experiences can further complicate the clinical diagnosis of depression in people with HIV (124).

A clinical diagnosis of depression is based on patient meeting the criteria for major depressive disorder set out in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The clinical diagnosis is defined by the presence of 5 out of a list of 10 symptoms, one of which must be depressed mood or loss of interest lasting for at least 2 weeks (94, 125). Depression is classified in the International Classification of Diseases (ICD) and Related Health problems, 10th Revision, as F:33.0.

As depression is based on patient reports of symptoms, several measures have incorporated the diagnostic criteria into a questionnaire format that can be administered by clinicians or filled out by patients themselves to serve as screening measures for clinical diagnoses of depression. Clinician-rated measures specific for depression include the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS) (126).

Generic PROMs for depression include the HADS subscale for depression (HADS-D), Patient Health Questionnaire (PHQ), Beck Depression Inventory (BDI), Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS) and Zung Self-rating Depression Scale (SDS) among others. Studies have also used generic HRQOL measures such as the EQ-5D, General Health Questionnaire (GHQ), and the Patient Health Questionnaire depression module (PHQ-9).

Early detection of depressive symptoms in populations that are at high risk of experiencing mental illness is critical to reducing symptom burden and improving QOL. There is no evidence that any of the legacy PROMs used to access depressive symptoms were designed with patient input as most were adapted from clinician-rated measures (127). It is indicated that both clinician-rated measures and PROMs for depression should be used when completing an assessment of depression

(126). More recently, two PROMs, PRO MDD for major depressive disorder and the Symptoms of Major Depressive Disorder Scale (SMDDS) provided evidence that the content of these measures reflected the experience of the target respondents (128-130). The key domains identified using this approach included emotional, cognitive, motivation, work, sleep, appetite, social, activities of daily living, fatigue, body pain and suicidality as relevant to depression for patients (130).

1.4.3-Measures of anxiety symptoms

The general measures of anxiety and severity of the symptoms are SRO measures and include the HADS subscale for anxiety (HADS-A), State Trait Anxiety Index (STAI) and Beck Anxiety Inventory (BAI) (131). Other measures of anxiety are intended to identify a specific anxiety disorder as characterized using the DSM-5 criteria (131). Measures of anxiety are also often used in the rheumatologic populations (131). HADS-A has been validated for use in medical conditions while the other two measures have been validated in geriatric and psychiatric populations (131). HADS-A has the strongest psychometric properties and is responsive to change (131). Self-reported symptoms are vital for the identification, clinical diagnosis, monitoring and the treatment of anxiety disorders (83). The use of PROs and the identification of the symptoms associated with anxiety is of critical importance to the clinical diagnosis of anxiety disorders (83). It is argued that due to the high relevance of the symptoms of anxiety, these can be useful as outcome predictors for anxiety (83).

1.4.4-Measurement approaches to cognitive ability

Both SROs and PerfOs (termed behavioural measures in psychology field) are used to assess cognitive brain health outcomes. Several authors have commented on the lack of overlap between these measurement approaches (132). In psychology, SROs and behavioural measures of the same construct were shown to be weakly correlated across a series of domains (133). Many behavioural measures were developed to produce replicable experimental effects for within-person comparisons which inherently reduces their usefulness or accuracy for between-person or correlational comparisons (133).

The reliability is also affected by a high error-variance which can be due to trial-by-trial variation in performance, especially, when the number of trials is limited which is typical of most behavioural measures (133). Also, error variance is increased by situational factors such as the emotional state of the person performing a task or taking a test, noise, illumination, distance from the screen, the presence of other people and so on (133). Some behavioural measures attempt to improve reliability, but this does not improve the correlations with SROs.

Despite having the same name, behavioural measures and SROs may actually measure different response processes (133). SROs ask people to reveal on their behaviours across several unstructured real-life situations, whereas behavioural measures draw on responses to less common stimuli in a specific and highly structured situation (133). Behavioural measures tend to rely on reaction on times and errors whereas SROs rely on the person's self-evaluation of about their performance rather than performance itself (133).

The +BHN cohort considered cognition as an ability and developed two measures to quantify this ability on a scale with interval-like properties. Communicating Cognitive Concerns (C3Q) is an SRO developed specifically for people with HIV, although it has also been shown to have similar measurement properties in the general population (134-136). It measures self-reported cognitive ability.

The Brief Cognitive Ability Measure (B-CAM) is a PerfO, a short battery of 8 cognitive tasks (137) that have been combined as a single construct using Rasch analysis and yields a continuous value for cognitive ability (93, 137-140). The B-CAM is mapped to the standard normal distribution a cut-point at the mean and higher values indicating more ability (141, 142).

The C3Q is likely to be more closely associated with the areas self-nominated on the PGI. Studies show that performance-based measures of cognitive ability are more likely to be associated with each other and less likely to be directly associated with SROs (132, 143).

1.5-Conclusion

This chapter presented an overview of the brain health outcomes that will be the focus of this thesis. The overview focused on how these brain health outcomes are traditionally measured along with the strengths and limitations of these approaches. This sets the stage for introducing the use of an individualized approach to mine textual data with the objective of identifying early indicators of brain health concerns.

CHAPTER 2: An individualized measure - The Patient Generated Index

2.1-Introduction

In the previous chapter, the notion of individualized and fully standardized measures was introduced. A widely used individualized measure is the Patient Generated Index (PGI) which was conceptualized as a measure of quality of life (QOL) (144). The theoretical basis for the PGI comes from K. Calman, who defined the QOL as "the extent to which our hopes and ambitions are matched by experience (145, 146)." The PGI was designed as a patient-centered individualized outcome measure that provided an alternative to the traditional approach of measuring disability and impairment by taking a focus on the assessment of overall QOL from the patients' perspective (146). This measure allowed respondents to individually define and quantify HRQOL in their own terms (147).

Mayo and colleagues have published extensively on the PGI across health conditions including preliminary data on the Positive Brain Health Now (+BHN) cohort (148-151). The PGI has the potential to be used in a wide range of clinical conditions due to its ability to quantify the effect of a health condition on an individuals' QOL (144).

The PGI is an individualized measure developed to assess the impact of a health condition on QOL (144). PGI consists of three steps: (1) nomination of the top 5 areas of life affected by the health condition; (2) rating the severity of these 5 areas plus a sixth area for all other aspects affecting QOL using a scale from 0 to 10, where 0 is as bad as possible and 10 is as good as possible; and (3) distribution of 12 tokens among all 6 nominated areas based on the importance for improvement, with more tokens spent on areas that the participant would most want to see improved. A global index score is calculated by multiplying the severity score (step 2) by the proportion of the 12 tokens allocated to that area and summing over the six areas, where 0 is poorest possible QOL and 100 represents best QOL. Figure 1 presents the general format of the PGI.

Figure 1: The Patient Generated Index and its components (administered to the +BHN cohort)

Patient Generated Index Scoring Sheet
Ask the participant to describe how HIV affects their life and activities.Please record the answers in the following table.
**** Interviewer instructions**** *See page 3 for instructions on how to complete the sheet.*

Step 1: Identifying area Affected by HIV	**Step 2: Scoring each area**	**Step 3: Spending points**
All other aspects of your life not mentioned above		

Step 1
Questions for the participant:
Think about the aspects of your life that are most affected by HIV.Give us at least five answers.

Instruction for the interviewer:
Write the answers in the boxes.

Step 2
Questions for the participant:
Value the areas you identified in Step 1.
Refer to the last month to determine the value.

Instruction for the interviewer:
Show the participant the scale from 1 to 10 and write the answers in the boxes.

Step 3
Questions for the participant:
Imagine what aspects of your life you would like to see improved. We give you 12 imaginary points that you need to place in the boxes based on your desire to see this aspect improved. The more you wantthis aspect to be improved, the more points you put in and the less you care about this aspect, the less you put in! You must include in your calculation the last option (6) “All other aspects of your life that you did not mention”. You are not obliged to put points in each box but this must give a total of 12 points. You cannot give less or more than 12 points in total!

Instruction for the interviewer:
Write the answers in box 3 and be sure not to exceed the 12-point limit.

The +BHN team has published extensively on the PGI including preliminary data on the cohort (150). In this study, only the text threads were analysed and not the other components yielding values for QOL. In previous work on the first 690 members of the +BHN cohort (150), the PGI score was 53 on average (SD: 24). This is in contrast to 82, 69, 70 and 75 on other standardized measures of health-related quality of life (HRQOL) and health when all were scored out of 100. Standardized measures tend to poorly discriminate between the heterogeneity in HRQOL across health conditions (150). The overlapping symptoms of HIV and somatic depression can inflate scores on standardized outcome measures (152, 153). More recently, patient-reported data has been shown to result excellent predictive values for depression in large cohorts; for example, a c-statistic of more than 0.80 was reported in people with diabetes (154).

A closer look at the life areas nominated by people with HIV shows that many of these areas are more closely related to ‘invisible’ disabilities such as the brain health concerns of psychological distress, depression, anxiety, and low cognitive ability. The correlations between the PGI and other standardized measures of HRQOL were reported to be the lowest for people with HIV and cancer(<0.33) across four conditions (150).

Thus, the PGI as an individualized measure can reflect on those aspects of QOL that are important to patients and in which they value an improvement.

2.2-Domains nominated on the Patient Generated Index

With the future of care delivery shifting towards a person-centered and evidence-based model (155), there is an emphasis on taking a closer look at the key areas nominated on the PGI. For people with HIV, many of the areas nominated on the PGI relate to physical, psychological or emotional health and relationships and the PGI meets the criteria for a best measure for the fourth 90 due to its focus on the areas that are important to the patients’ HRQOL (156). Thus, the PGI is suited to inform the design of the care programs aligned with the needs of people with HIV.

Complete responses for the PGI were obtained for about 80 percent of the participants with higher response rates when using interviews as compared to questionnaires (157, 158). For the +BHN cohort, the completion rates were higher at 93% (798 out of 856). Few studies have utilized the PGI to identify the most important domains for people with HIV including one in Canada by the +BHN team (150) (n=690), another in Thailand (n=210) (159) and recently one in Kenya (156). People with HIV were more likely to nominate areas related to quality, cost, and accessibility of healthcare and rehabilitation services in the developing world context. The key non-health domains included expenses related to hospital visits, cost of living, work status, productivity, social stigma, family responsibilities and a lack of family support (159).

Table 1 summarizes the literature for the most common life areas nominated on the PGI (in order of prevalence) across different chronic concerns reported by people in the developed countries (148, 150, 160-165). In people with HIV, an interesting observation was that a majority of life areas nominated on the PGI were sentiments associated with brain health concerns (i.e., health, emotional function, intimacy, relationships, stigma, perception of self or body image, cognition and fatigue) (150). Areas not regarded as sentiments were incorporated in the measurement model as other predictors of physical function, work status and satisfaction with sexuality. The ability to work was amongst the top concerns in people with HIV even when the HIV was well-treated while mild cognitive impairment was associated with work-related difficulties (166).

Table 1: Top areas or domains nominated on the PGI in the developed country context

Amyotrophic lateral sclerosis (n=52), 3 sites across Canada	**Cancer (n=192), Montreal, Canada**	**Chronic heart failure (n=59), Dundee, UK**	**Chronic pain (n=65), Montreal, Canada**	**Chronic obstructive pulmonary disease (n=270), Ontario, Canada**	**HIV (n=691), 5 sites across Canada**	**Low back pain (n=80), Norway**	**Multiple sclerosis (n=185), Montreal, Canada**	**Pakinson's disease (n=76), Montreal, Canada**	**Stroke (n=249), 11 sites across Canada**	**Systemic sclerosis (n=62), Houston, USA**
Recreation and leisure	Fatigue	Walking	Recreation and leisure	Mobility	Health	Pain	Work/school	Dexterity	Walking /mobility	Ability to participate socially
Lower limb mobility	Sleep function	Problems with daily activities	Global mental functions (sleep, self-esteem)	Recreation and leisure	Emotional function	Sleep	Fatigue	Walking	Arm impairment	Social relationships
Interpersonal relationships	Pain	Tiredness /sleepiness	Work and employment	Domestic life	Intimacy	Stiffness	Sports	Sleep	Work	Activities of daily living
Self-care	Appetite	Stairs/inclines	Household tasks	Interpersonal relationships	Work/school	Socializing	Social life	Fatigue	Recreation /leisure	Physical activity
Housework and preparing meals	Emotional function	General health/medical conditions	Walking and moving	Mental functions	Relationships	Housework	Relationships	Cognition	Driving	Cognition
Speaking	Work	Social life	Specific mental functions (cognition and mood)	Work and employment	Recreation /leisure	Work	Walkiing	Tremors /Dyskinesia	Vigorous activities /sports	Self-efficacy
Eating and swallowing	Recreation and leisure	Hobbies and interests	Changing /maintaining body position	Carrying /lifting objects	Stigma	Walking	Cognition	Sports	Speech	Psychosocial illness effect /negative mental health
Work and employment	Social life	Pain /discomfort	Genital and reproductive functions	Self-care	Perception of self /body image	Morning /getting started	Balance	Depression /Anxiety	Housework	Fatigue /energy
Upper limb mobility	Eating	Independence	Interpersonal relationships	Changing /maintaining body position	Cognition	Exercise /physical activity	Housework	Self-care	Balance	Sexual function
Daily routine and independence	Family relationship		Eating	Environment factors	Exercise tolerance	Travelling	Mood	Speech/voice	Memory	Upper extremity /physical health
	Mobility				Fatigue	Family relations				Mobility

An overarching theme observed in oncological settings was that the domains nominated on the PGI were not always detected by standardized measures of QOL (147). The potential implications of permitting people to characterize their QOL on their own terms are immense (147). In advanced cancer, patients were able to express a wide range of QOL concerns on the PGI and the score was 25 to 30% lower compared to the scores documented through other standardized measures, especially when the QOL was poor (148). Similarly, people with cancer focused exclusively on the negative impact and its treatment, showing that the type of permissible answers based on the words used in the PGI and instructions may be skewed towards negative areas that impact the HRQOL (167). Differences in the scores between the standardized measures and the PGI were also observed for people with HIV (150). Such differences in the nominated domains may explain the low correlations between the PGI and other measures of QOL.

The triangulation of both The International Classification of Functioning, Disability and Health (ICF) and the Patient-Reported Outcomes Measurement Information System (PROMIS) frameworks identified 10 core PRO domains to include for chronic pain: pain interference, physical function, sleep disturbance, anxiety, depression, ability to participate in social roles and activities, fatigue, sleep-related impairments, and self-efficacy (99, 160). About three-fourth of the domains nominated on the PGI by individuals with chronic pain included recreation and leisure, global mental function, work and employment, household tasks and walking and moving (160). The domains on standardized measures were identifiable along with the areas that were most important to the patients. The PGI provides more information on the heterogeneity of life areas that need to be considered by preference-based measures of QOL for specific conditions (168).

2.3-Psychometric properties

More recently, a systematic review identified 69 studies that reported on the psychometric properties of 30 PROMs used to measure HRQOL in people with HIV (169). Most assessed the psychometric properties of Medical Outcomes Study HIV Health Survey (MOS-HIV), the brief version of the World Health Organization’s Quality of Life Instrument in HIV infection (WHOQOL-HIV-BREF), 36-Item Short Form Survey (SF-36) and Multidimensional Quality of Life Questionnaire for Persons with HIV/AIDS (MQOL-HIV) (169). These centered on content validity, construct validity and internal consistency with a limited focus on cross-cultural validity, criterion validity, reliability, hypothesis testing and responsiveness (169).

2.3.1-Validity

As mentioned earlier, the PGI has 3 components: nominating areas, severity rating, and priority weighting. Most studies on the psychometric properties of the PGI have focused on relationships between the total PGI score and other measures of QOL or HRQOL (144, 146, 157, 170-175). For this study, the emphasis was only on the areas nominated and not the total scores. In the context of rheumatoid arthritis, people who nominated an area as affecting their QOL using the PGI also spontaneously raised these areas in an interview (176). In Ankylosing Spondylitis (AS), the areas nominated were all represented on a well-known standardized measure (177). Other research has shown that those who nominate an area will also score lower on standardized tests or measures of related constructs (149, 151, 178).

2.3.2-Reliability

Test-retest reliability of the PGI is difficult to assess as the number of possible areas is very large and when the person is asked to name only 5, it is likely that different life areas will be nominated as the person has time to reflect on their answer (179). Over a two-week period, one-third of the sample changed only 0 or 1 area, and another one-third changed over 2 areas (177). In the presence of a catalyst, a change in the areas nominated can indicate a response shift (179, 180). In people with rheumatic conditions, the test-retest intraclass correlation coefficient (ICC) of the PGI were in the range of 0.86-0.87 for the PGI scores for the 5 life areas nominated on the PGI over a 1-year interval (158, 181). The PGI was easy to administer and moderately reliable with an ICC of 0.72 in an elderly cohort (182).

CHAPTER 3: Sentiment analysis and brain health concerns

3.1-Background

A sentiment is an attitude, thought, or judgment prompted by feelings (183) or a general feeling about a situation (183, 184). In computer science literature, sentiments are defined as opinions or feelings that people express and are manifested in terms of polarity (i.e., positive, neutral or a negative) (185, 186). Sentiment analysis or opinion mining is the automatic processing of sentiments, opinions, and subjectivity within textual data (187). Emotion recognition and sentiment analysis are important areas in natural language processing (NLP) (188). Emotion detection is the means to identify distinct human emotion types, while sentiment analysis is associated with the detection of polarity (188). These terms are often used interchangeably for the identification of human emotion types and for the detection of polarity.

The emotional state of an individual may also have physical manifestations that are visible such as sweating, heart rate, shivering of hands and changes in the pitch of the voice (188). Thus, sentiment analysis can also include categories that are indicative of these somatic or medical references (i.e., sleep problems, physical pain, skin colour) (189). Such a categorization is contextualized from the evolution of the definition of the word 'emotion' from the 17^{th} century to the present day. The term 'emotion' was initially described as a physical disturbance and came to be known as a psychological term in the 19^{th} century (190).

Sentiment analysis is possible at the document, sentence and aspect level (188). At the document level the task is to determine the overall opinion of the document on a single entity (187). At the sentence level it aims to classify the overall polarity of a sentence or if each sentence has expressed an opinion (187). Aspect-based sentiment analysis is performed at a finer level and is characterized both in terms of polarity and the targeted aspect. For the Positive Brain Health Now (+BHN) cohort, sentiments expressed through the Patient Generated Index (PGI) text threads were annotated to each aspect with a known or specified polarity.

3.2-Sources of information on sentiments

One major source of written text that can inform sentiments at the individual, group, or at the population level comes form social media mining. People share a plethora of personal experiences within their private networks and across social media forums that are often publicly accessible (188, 191). Such an exchange creates a large library of textual data which can be used to examine recurring topics (188, 192, 193). Analyzing such information forms the basis for identifying the high-risk sentiments associated with brain health outcomes. Sentiments known to be associated with brain health outcomes in the general population are referred to as high-risk sentiments. Now, it is equally important to identify, develop and use the sources of data from the clinical settings to further test and validate the predictive ability and replicability of such results in different populations such as for people with Human Immunodeficiency Virus (HIV).

Obviously, there are no rules for communicating sentiments across individuals and platforms which presents a multitude of challenges in using such information. Examples of such challenges include dealing with the context, lexical and syntactical uncertainty, scorn, statements that contain a mix of emotions, and the identifying the Web slang to ensure appropriate analysis (188).

More recently, information available from social media accounts (Facebook, Twitter etc.) of patients clinically diagnosed with depression was used to conduct a retrospective analysis of their social media imprint to determine if such an outcome could have been predicted early-on (188, 189). Nevertheless, the availability of a small sample size in these studies was a key limitation of this integrated approach.

Thus, having textual data collected from the clinical settings, such as the life-areas nominated on the PGI can provide researchers with targeted information for a large cohort. Such textual data can be useful in predicting the presence or emergence of brain health outcomes early-on during the clinical encounter.

3.3-Applications in health and well-being

Sentiment analysis applications in healthcare are concentrated on the physical, mental, and social well-being of people rather than diseases, injuries, and disabilities (193). Well-being is considered a perceived or subjective state and quality of life (QOL) does not necessarily depend on the absence of symptoms (194). Sentiment analysis for patients with chronic conditions focuses on the extent to which the associated symptoms are managed or controlled. Predicting "invisible disabilities" such as depression, anxiety and overall mental health remain popular themes in sentiment analysis research (193, 195-200).

Sentiment analysis has been applied to the context of a wide range of health-related concerns such as cancer (201-203), mental health (204), addiction (205), pain (206), infectious diseases (207), QOL (208), and joint and muscle pain (209). Predicting the emergence or presence of depression is a common theme used to validate sentiment analysis techniques (195, 196, 210). Other mental health concerns predicted via sentiment analysis include suicidal ideation (211), dementia (212) and the impact of coronavirus on the overall mental health of social media users (213).

Several papers focus on chronic conditions including diabetes (214), Chron's disease (215), multiple sclerosis (216), and asthma (217). Many have also studied obesity (218), anorexia (219) and other eating disorders often associated with self-focused attention (SFA), rumination, and body image issues referred to as depressogenic schemata or cognitive predictors of depression and anxiety. More recent studies enquire, among active social media users, to what extent sentiment analysis can be used to predict mental health concerns, about 3 to 6 months prior to the initial clinical diagnosis.

3.4-Computerized approaches to sentiment analysis

Approaches to sentiment analysis include lexicon-based, machine learning, hybrid, and other methods such as transfer learning and aspect-based techniques. Lexicon-based approaches are unsupervised and do not require a training data. Such approaches use either a dictionary or a corpus for determining the polarity of the text and are feasible at the sentence and feature level. Such an approach is domain focused and mutually exclusive which can be either a strength or a limitation of the approach depending on the type of analyses required. A corpus-based approach employs semantic and syntactic patterns to ascertain the emotion of a sentence (i.e., collection of written texts, temporal categories, entire works by authors) while dictionary-based techniques adopt statistical or semantic approaches.

Machine learning which is regarded as a sub-field of artificial intelligence (AI) enables systems to learn on their own to generate data-driven predictions by developing models that discover patterns and use those to generate predictions. Machine learning is increasingly popular for sentiment analysis and includes techniques such as the decision trees, linear classifiers, rules-based classifiers, probabilistic classifiers, and the K-nearest neighbour. Linear classifiers such as the neural networks are increasing being utilized in machine learning research (220, 221). AI-based transformers, which are neural networks that use deep learning to make accurate predictions, recently approached the theoretical upper limits in terms of accuracy, effectively converging with the psychological rating scales (220). The best performance is attained using trained human or crowd coding while dictionary-based techniques often fall short of human performance (222). Thus, automatic text analysis methods should always be validated (222).

3.5-Category coding

Most research performs sentiment analysis on binary scales for the categorization of sentiments such as the use of positive and negative, agree or disagree, and good or bad categories (188). Some researchers have used a categorical scale from 1 to 5 when the differences between sentiment polarity or sub-categories are evident (223, 224). More recently, researchers have also assigned weights to different sentiments (225). Thus, it is imperative that the scale best suited to the textual data is used to optimize the use of available information when possible.

Psychological models that incorporate emotions are classified as dimensional or categorical. The dimensional models represent emotions based on valence, arousal, and power (188). Valence indicates polarity, arousal signifies the level of excitement within a feeling, and power indicates the level of restriction over emotion (188). The categorical models generally classify emotions into four, six or eight categories (188). My thesis develops a framework for sentiment analysis with six high-risk sentiment categories (emotional, interpersonal, somatic, depressogenic, anxiety and cognitive sentiments) annotated at the aspect-level and a seventh category for positive sentiments, hypothesized to be protective of brain health.

3.6-High risk sentiments associated with brain health concerns

Within the psychological literature, sentiments associated with brain health concerns are often identified using a case-based approach (226). Seminal papers used linguistic methods and text analysis to enable an understanding of the lived experience from the patient's perspective. A sense of apathy and inner turmoil is often associated with depression in such approaches (227). An important milestone in sentiment analysis research related to health and well-being was the classification and categorization of individual sentences from a compilation of suicide notes left by people; this included the identification of an array of emotions associated with brain health challenges (193). A majority of the 19 studies that published their results after developing different classification systems utilized user-generated content from the social media to validate their classifications and to access their performance (193).

The language predictors of depression comprise of depressed mood, loneliness, anger, hostility, somatic or medical references, and emotional, interpersonal, and cognitive processes (189, 228). Sadness was identified as the primary emotional predictor of depression, while loneliness and hostility were the key topics associated with interpersonal predictors (189). Linguistic cues to express negative emotions include trigger words (i.e., worthless, loss, hurt and more) (195, 229). Particularly, sadness (i.e., crying, grief and sad) and anger (i.e., annoyed, stop, hate, kill) were expressed by people more likely to be depressed (195). Positive sentiments (i.e., joy, love, nice) were protective of the symptoms of depression and relapse (195).

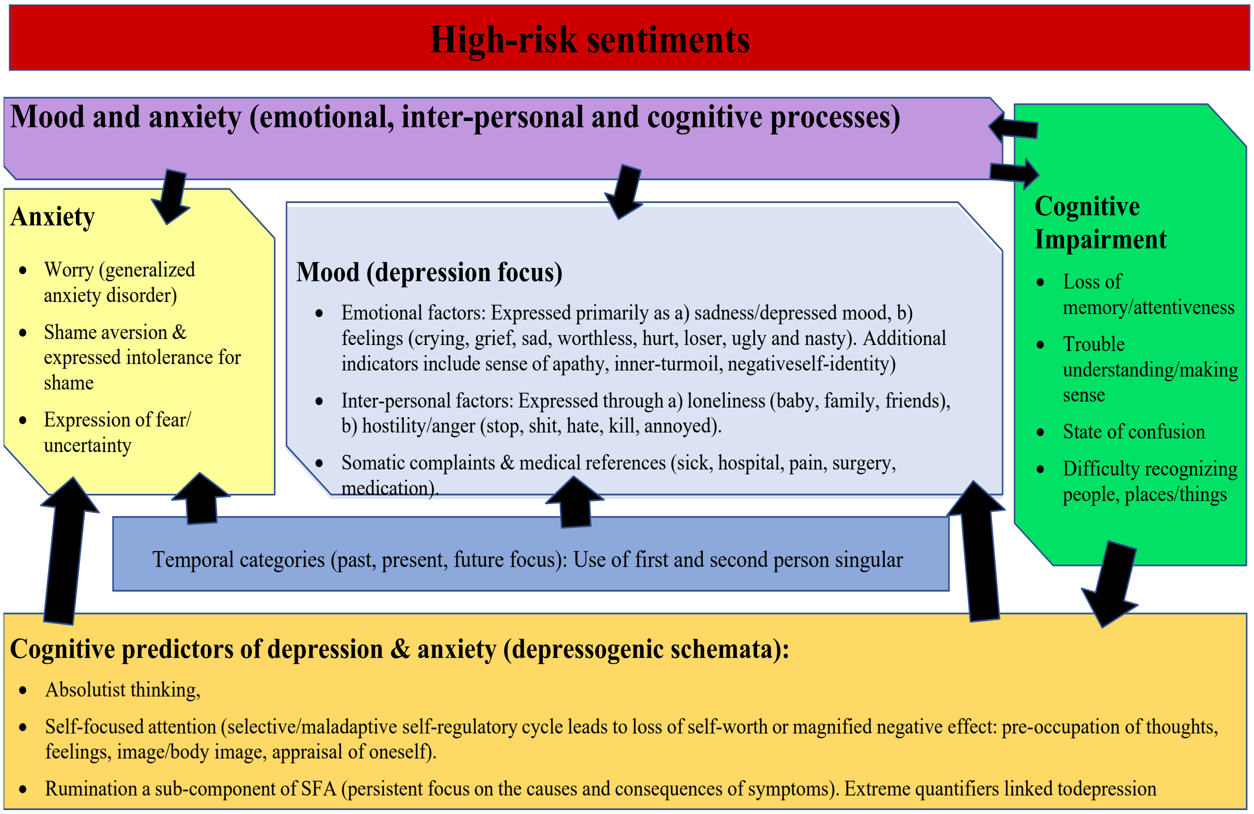
The key expressions associated with the generalized anxiety disorder (GAD) were fear (195), worry and intolerance for shame (230). Shame aversion was also associated with worry (230). Other less understood elements associated with specific disorders, or several psychological conditions included SFA (231). More recently, studies have identified several expressions and linguistic patterns used in daily life that may indicate underlying brain health concerns (232). Themes and topics associated with mal-adaptive psychological processes referred to as depressogenic schemata include absolutist thinking, rumination and SFA (232-234). Also, depression and anxiety may be expressed in the form of absolutist thinking and expressions with extreme quantifiers such as everything, always, nothing, and never are forms of absolutist thinking are often associated with depression (227, 235).

A selective SFA includes pre-occupation of thoughts, feelings, images, or appraisals about oneself (236). This awareness about the self may be counter-productive when there is a considerable discrepancy between the ideal and the actual self (232). Eating disorders associated with body image may be driven through a mal-adaptive self-regulatory cycle leading to a magnified negative affect and a loss of self-worth (232, 236). Similarly, a pre-occupation with the self and rumination are also referred to as the cognitive predictors of depression (189, 231, 237). Rumination is defined as a pattern of responses to distress that result in an individual to persistently focus on symptoms and the possible causes and consequences of their symptoms (232). On the contrary, clinical evidence shows that SFA may not be unique to depression and is common to several brain health concerns (229).

The use of temporal categories (i.e., a focus on the present, past, or future) is also associated with brain health concerns (195, 226). The use of first person singular may be moderated via SFA or rumination and is associated with depression (238). The use of second person singular by a writer who committed suicide was also associated with depression (227). Textual analysis of the essays written by formerly depressed students demonstrated a link between current depression and negative sentiments (238). More recently, the same pattern was identified for depressed users on social media forums (239).

Depressive symptoms are often associated with a negative identity and emotions shape the self-identity of an individual (240). The use of a patient-centered measure to identify high-risk sentiments can reduce the emotional distance between the self and the patient (241). The predictive ability of such sentiments can be contextualized in terms of the patterns identified in verbal communication (242). A linguistic analysis of patients with mood and anxiety disorders performed during cognitive behavioural therapy (CBT) identified the differences in the emotional foci of the patients experiencing either depression or anxiety (242). Depressed patients were more likely to use words related to sadness, while SFA was a characteristic within both groups (242). Similar patterns have emerged in both written and verbal linguistic analysis that further confirms the evidence on high-risk sentiments. Figure 1 summarizes the sentiment categories associated with depression, anxiety, and cognitive impairment.

Figure 1: High-risk sentiments associated with brain health outcomes



3.7-High-risk sentiments in people living with HIV

Although, few have conducted sentiment analysis specific to people with HIV there are studies that identify life-areas classified as high-risk sentiments for this segment of the population. A meta-analysis showed that disclosure and social support were positively associated while stigma was negatively associated with both disclosure and social support in people with HIV. Stigma, privacy concerns and social discrimination played a major role in an online HIV community in China (243).

The etiology of depression in people with HIV is associated with biological factors, psychosocial factors and the history of comorbidity of psychiatric illness (244). Depression is also associated with HIV-infection and disease progression (245). Depending on the population and the measure used to assess depression in people with HIV, its prevalence ranges from 18-81% (244). Similarly, the prevalence of major depression in aging people with HIV (>50 years of age) in a large cohort study was estimated to be 39.1% (246). Notably, HIV-associated stigma, loneliness, energy levels, age and cognitive functioning explained 42% of variance in depression (246). Evidence shows the role of stigma as a predictor of mental health and its association with race and gender in people with HIV (247). Also, the emotional effects of adherence demand, treatment burden of antiretroviral therapy (ART), sexual health issues, relationship dynamics, self-image, change in body weight, and social support are associated with depression in HIV.

3.8-Conclusions

Evidence supports the value of natural language in predicting brain health outcomes. More recently, studies have corroborated the psychological theories associated with depression and enable an understanding of the high-risk sentiments within this framework. The ability of textual analysis to identify early-risks from user-generated content presents an opportunity to apply sentiment analysis to the PGI. Sentiment analysis has been widely applied to mental health concerns and to people living with chronic conditions.

My thesis uses the high-risk sentiments to predict brain health outcomes for the +BHN cohort. A broader context of brain health is adopted to include cognitive ability which has been largely excluded in the previous studies; such an approach is counterintuitive as depressogenic schemata (the cognitive predictors of depression and anxiety) are important topics in sentiment analysis. Furthermore, my study addresses other limitations by including a large cohort from the clinical settings and with longitudinal data spanning over a 27-month period to predict the presence and emergence of brain health outcomes.

CHAPTER 4: Objectives and rationale

While there is no cure, the Human Immunodeficiency Virus (HIV) infection has become a manageable chronic health condition. A growing mental health burden on this aging population presents challenges that need to be confronted. About 10.7% of the global population has mental health disorders with when compared to 38.6% reported in people with HIV in a Canadian cohort (22) and prevalence rates for current major depression at 3.1 times higher when compared to the general population in a pooled United States cohort of people with HIV (24, 114). Higher prevalence of brain health concerns in people aging with HIV are associated with the long-term fatigue from the psychosocial factors associated with the condition, social stigma, sexual dysfunction, reduced physical function, and neurobiological changes (17, 22-25, 30-34).

This study identifies a "semi-qualitative" approach that could be used as an early-warning system to identify the self-nominated areas related to mood, anxiety, and cognition on the PGI that are associated with a greater prevalence of brain health outcomes. More recently, studies have shown that emotional, anxiety, and cognitive symptoms are associated with depression and mental health (193, 195, 196, 210). Thus, the primary objective of this thesis was to estimate the extent to which a self-nomination of areas related to mood, anxiety and cognition on the PGI predict the presence or emergence of psychological distress, depression, anxiety, or cognitive impairment among people with HIV at the first assessment at study entry and for successive assessments over 27-months. The secondary objective of this study was to estimate the extent to which a self-nomination of areas related to mood, anxiety, and cognitive sentiments on the PGI are associated with a greater prevalence of brain health concerns among people with HIV.

This study considers the interaction among all important indicators of brain health to include sentiments related to mood, anxiety, and cognition with the objective of predicting psychological distress, depression, anxiety, and cognitive difficulties. More recently, studies have used text analytics gathered from social media of patients diagnosed with depression to develop an early-warning system to predict depression. Instead of relying on data from social media forums which is often scarcely available for consenting patients diagnosed with a brain health condition, this study explores a more direct approach of using the textual data collected from patients using the PGI to predict brain health outcomes.

CHAPTER5: MANUSCRIPT 1

The Patient Generated Index (PGI) as an early-warning system for predicting brain health challenges:

A prospective cohort study for people living with Human Immunodeficiency Virus (HIV).

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Abstract

Background: In research people are often asked to fill out questionnaires about their health and functioning and some of the questions refer to serious health concerns. Typically, these concerns are not identified until the statistician analyses the data. An alternative is to use an individualized measure where people are asked to self-nominate areas of concern which can then be dealt with in real-time. The relevance of this approach to identify brain health concerns has not been explored in people aging with HIV.

Objective: To estimate the extent to which self-nominated areas related to mood, anxiety and cognition on an individualized measure of quality of life (QOL), the Patient Generated Index (PGI) predicts the presence or emergence of depression, anxiety, psychological distress, or cognitive impairment among people with HIV at study entry and for successive assessments over 27-months.

Methods: The data comes from participants enrolled in the Positive Brain Health Now (+BHN) cohort (n=856). The nominated areas were category coded to a sentiment framework. A longitudinal design was used to link self-nominated sentiments to presence or emergence of anxiety, depression, or cognitive impairment as assessed using standardized measures of these constructs. Logistic regressions were used to estimate the goodness of fit of each model using the c-statistic.

Results: The sentiments categorized as 'emotional' predicted all of the brain health outcomes at all visits with adjusted odds ratios (OR) ranging from 1.61 to 2.00 and c-statistics >0.73 (good to excellent prediction). Nominating an anxiety sentiment was specific to predicting anxiety and psychological distress (OR: 1.65 & 1.52); nominating a cognitive concern was specific to predicting self-reported cognitive ability (OR: 4.78). Positive sentiments were predictive of good cognitive function (OR: 0.36) and protective of depressive symptoms (OR: 0.55).

Conclusions: This study indicates the value of using this semi-qualitative approach as an early-warning system in predicting brain health outcomes from the spontaneously nominated life areas obtained by administering the PGI.

5.1-Introduction

People involved in research projects are often asked to fill out questionnaires about their health and functioning. It is common that these questionnaires contain items that reflect serious health concerns. Typically, these concerns are not identified until the statistician analyses the data. Several processes have been put in place to make this process more streamlined and responsive, but they are all dependent on a data capture platform and so delays in data processing are common.

In clinical practice, the brain health concerns of patients are mostly identified without standardized methods although the use of patient-reported outcome measures is recommended and increasingly used (1). There are limitations in using patient-reported outcome measures (PROMs) in clinical practice (2) and no one measure may fit all the concerns patients may have.

This study tests whether a “semi-qualitative” approach could be used as an early-warning system in predicting the presence or emergence of brain health outcomes. Brain health has been defined as a multi-dimensional construct reflecting the brain’s role in cognition, mood, emotional stability, motivation and energy (3, 4). These outcomes are sometimes termed as the “invisible disabilities (5)” because they are not accompanied by physically observable impairments. They are elicited through a personal interview conducted by a trained health professional or by administering standardized questionnaires that have been developed for this purpose (6). The former is resource intensive, and the latter requires data processing and interpretation, processes that are not always clinically timely.

An individualized measurement approach could be a feasible way of obtaining rich interview data as well as quantitative data useful for research and monitoring change in those areas that most matter to patients. The Patient Generated Index(PGI) (7) is an individualized or personalized measure which asks people to spontaneously nominate life areas related to their condition that affects their quality of life (QOL). These areas are severity rated and prioritized quantitatively. This measure takes under 5 minutes to complete and could easily be done in clinical or research context. One of the concerning health conditions that could be detected using this method is depression. In the context of brain health, other concerning health states are anxiety, psychological distress and cognitive difficulties.

Although the PGI has immense potential for use in clinical and research settings, it is important that the information gathered has a similar interpretation to the information gathered using standard procedures for obtaining this information. For example, in people with advanced cancer, use of the PGI allowed patients to voice a wide range of QOL concerns including many areas that were not assessed by standard QOL measures (8-10). In addition, when areas nominated using the PGI had matching items on a standardized measure like the RAND-36 (11), information was comparable. The PGI has also been shown to yield interpretable information about mental health status of people with severe mental illness (12), hospitalized older persons (13), and in people with brain injury (14).

In HIV, the PGI could be particularly useful as many of the health experiences relate to brain health outcomes and are "invisible"; to adequately assess them would require a lengthy interview and/or a large number of questionnaires to be administered and interpreted. While the PGI has been used in HIV, its use was confined to generating the most impactful life areas, and among the top 10 were emotional function, cognition, and fatigue (15). The relationship between the brain health areas nominated and results on the standardized measures has not been investigated in the HIV population and would be valuable information to support the clinical usefulness of the PGI.

The qualitative output of the PGI is unstandardized text threads which need processing in order for the persons' concerns to be accurately identified. In the work by Mayo and colleagues (4, 11, 16-21), the text threads emerging from the PGI were mapped to the World Health Organization's International Classification of Functioning, Disability and Health (ICF) using a process called category coding. However, a closer examination of the content of the text threads from people with HIV describing the areas of concern shows that these areas are not so much about physical disabilities but rather about sentiments. Sentiments are defined as an attitude, thought, or judgment prompted by feelings (22) or a general feeling about a situation (22, 23) and are manifested in terms of polarity (i.e., positive, neutral or a negative emotion) (24, 25). Sentiment annotation is the labeling of emotions, opinions, or polarity of the sentiment inherent within textual data (26). Annotation of free text describing the areas of concern was more appropriate than category coding along the framework of the ICF. The analysis of sentiments, whether automated using natural language processing (NLP) (27) or by annotation, aims to identify areas of physical, mental, and social well-being rather than diseases, injuries and disabilities (27).

Therefore, the purpose of this study was to estimate the extent to which nominating life areas related to sentiments expressing emotional and/or cognitive concerns as impacting QOL on the

PGI predicted the presence or emergence of depression, anxiety, psychological distress, or cognitive impairment among people with HIV at study entry and over successive assessments at 9-month intervals over 27-months.

5.2-Methods

A longitudinal study was carried out using data from participants enrolled in Positive Brain Health Now (+BHN) cohort (n=856). This cohort has been well described previously (4, 21, 28, 29). Briefly, cohort members were recruited between 2014 and 2016 from five Canadian sites and followed prospectively for 4 years at visits, 9 months apart. Participants were over 35 years of age at time of recruitment, living with HIV for at least one year, and without dementia, co-morbidity affecting cognition, substance abuse, or life-threatening illnesses.

Participants for whom the respective outcome data were available for the time points under study (study entry and at each successive assessment) were included.

5.3-Measures

The PGI is an individualized measure developed to assess the impact of a health condition on QOL (7). PGI consists of three steps: (1) nomination of the top five areas of life affected by the health condition; (2) rating the severity of these five areas plus a sixth area for all other aspects affecting QOL using a scale from 0 to 10, where 0 is as bad as possible and 10 is as good as possible; and (3) distribution of 12 tokens among all 6 nominated areas based on the importance for improvement, with more tokens spent on areas that the participant would most want to see improved. A global index score is calculated by multiplying the severity score (step 2) by the proportion of the 12 tokens allocated to that area and summing over the six areas, where 0 is poorest possible QOL and 100 represents best QOL. The +BHN team has published extensively on the PGI including preliminary data on the cohort (15). In this study, only the text threads were analysed and not the other components yielding values for QOL. In previous work on the first 690 members of the +BHN cohort (30), the PGI score was 53 on average (SD: 24). This is in contrast to 82, 69, 70 and 75 on other standardized measures of health-related quality of life (HRQOL) and health when all were scored out of 100.

5.4-Outcome measures

Three patient-reported outcome measures were used as indicators of depression, anxiety, psychological distress and cognitive impairment. The Hospital Anxiety and Depression Scale (HADS) was used to identify people who are likely to have clinical depression or generalized anxiety. The scale consists of seven items for anxiety (HADS-A) and seven items for depression (HADS-D); scores on the sub-scales range from 0 to 21, with a score ≥ 8 indicative of clinically important anxiety or depression (31, 32). The Mental Health Index (MHI) of the RAND-36(33) was used to identify people who are likely to have psychological distress (34). A cut-point of 60 or higher out of 100 was used to indicate good mental health (35).

Three measures were used to identify cognitive impairment, two self-report outcomes (SROs) (Perceived Deficit Questionnaire-PDQ and Communicating Cognitive Concerns Questionnaire-C3Q) and a performance-based outcome (PerfO), the Brief Cognitive Ability Measure (B-CAM). Initially, the cohort was assessed using the PDQ which comprises 20 items scored on a 5-point ordinal scale (0 to 4) yielding values ranging for 0 to 80, with 40 or more indicating cognitive impairment (17). The PDQ covers domains of retrospective memory, prospective memory, attention or concentration, and planning or organization (17). It was developed for use in people with Multiple Sclerosis (MS) and is one of only a handful of measures reflecting how the person perceives their cognitive challenges.

During the course of the +BHN cohort, a new measure, C3Q (16), was developed specifically to reflect the cognitive challenges experienced by people with HIV. The C3Q comprises 18 items measured on a 3-point ordinal scale that reflect memory, concentration, executive function, language, emotions and motivation (17), yielding scores ranging from 0 to 36. The C3Q replaced the PDQ in the later stages of the study.

Eight of the items from the PDQ overlap with the C3Q and the two measures are highly correlated (0.80) (17). Both measures were transformed to range from 0 to 100. The cut-point for cognitive impairment on the C3Q has not yet been determined and so the same one for the PDQ was used, 50 on a 0 to 100 scale.

The third measure of cognition was the B-CAM, a short battery of 8 cognitive tasks (36) that have been combined as a single construct using Rasch analysis and yields a continuous value for cognitive ability(4, 19, 20, 37, 38). The B-CAM is mapped to the standard normal distribution with a cut-point at the mean and higher values indicate more cognitive ability(4, 18).

5.5-Category coding to the sentiments

Tokenization is often used for sentiment analysis with the objective of separating a piece of text into smaller units often known as tokens (37). We used tokenization to identify the sentiments nominated by the +BHN cohort on Step 1 of the PGI at study entry, this process marked the sentiments as distinct from unrelated text. Sentiments were extracted and tokenized using annotation (38-40) and through the semantic representations identified via high-level human judgment (41-44). Negative sentiments were assigned to one of the six categories identified from the literature: emotional (i.e., depression, loss of freedom, burden), interpersonal (i.e., level of acceptance, isolation from others, separation from others), somatic (i.e., sleep problems, sensitivity to medication, loss of appetite), depressogenic (i.e., lack of confidence, less attractive, self-indulgence), anxiety (i.e., fear of rejection, worry, secrecy), or cognitive (i.e., memory, concentration, decision-making) categories. Since the PGI prompts respondents to nominate areas that impact their QOL, there is a tendency to nominate negative sentiments. Nevertheless, some participants also expressed positive sentiments which were assigned to a single category referred to as positive sentiments (i.e., advocacy, spirituality, hope). These categories were then dichotomized and classified as '1' when a sentiment was nominated one or more times, and '0' when a sentiment was not nominated.

5.6-Other predictors

The literature identifies several variables that contribute to brain health outcomes in HIV including age, sex, education, physical function, satisfaction with sexuality and work status (45-50). These variables are among the top domains or areas nominated on the PGI. Age is measured on a continuous scale; sex is categorized as binary; education is measured on a categorical scale from 1 to 5 with '1' representing no or only kindergarten and '5' being university education. Physical function was assessed on a binary scale with a score of <45/100 on the Physical Function Index (PFI) of the RAND-36 representing poor physical function (51). Satisfaction with sexuality was measured by a single question drawn from the WHOQOL-HIV-BREF and scored from 1 to 5 (52, 53). Work status is measured on a binary scale with individuals categorized as working when paid employment is at least 15 hours/week (54). Figure 1 depicts the theoretical framework of the measurement model applied to sentiment analysis.

5.7-Statistical analysis

The presence of high-risk sentiments was identified from the PGI at first assessment and linked cross-sectionally to each brain health outcome indicator at the same evaluation point. For the longitudinal component, the PGI sentiments from first assessment were linked to brain health outcome indicators and three later assessments, 9-months apart.

Generalized estimating equations (GEE) for binary response data, were used to link the sentiments identified from the PGI to the brain health outcome indictors at all time points. This method was used because the participants were enrolled from 5 different sites imposing a correlated data structure (55-57). A binomial distribution GEE model was used for binary outcome measures including the HADS-D, HADS-A, MHI and the PDQ/C3Q (58).

The odds ratio (OR), confidence intervals (CI), and the c-statistic for each unadjusted and adjusted model were estimated (59). The c-statistic quantifies the area-under-the-receiver-operating-characteristic curve (AUROC) which is a measure of the inherent discrimination ability of various predictors of an outcome (60-62). The c-statistic represents the proportion of all possible pairs of observations in which one pair has the outcome for which the predicted value for the one with the outcome is higher than the one without. Values range from 0 to 1, with 0.5 being equivalent to predicting by flipping a coin, 0.7 indicates acceptable prediction, greater than 0.8 is interpreted as excellent prediction and 1 indicates perfect prediction (63).

The c-statistic was calculated for all sentiment categories univariately and after adjusting important sentiments for other contributors of age, sex, work status, education, satisfaction with sexuality and physical function. Logistic regressions were used to predict all outcome measures except the B-CAM which was normally distributed and modelled using a linear regression model. All analyses were conducted in the SAS (previously "Statistical Analysis System") version 9.4. The Venn diagram used to depict the overlap of brain health outcomes was generated using the VENNY 2.1(64).

5.8-Results and analyses

A total of 797 people who assigned the 12 imaginary points to the nominated areas or aspects of life that they would like to see improved were included in the analyses. Table 1 presents the socio-demographic and clinical characteristics at study entry and at each successive assessment. The numbers of people and their composition in the +BHN cohort is shown as percentages in brackets. The mean levels of the HIV immune markers for the cohort are presented along with their standard deviations. At study entry, the cohort was composed mostly of adult men with a mean age of 52.9 years. Almost all participants had a high school education or more. Over half of the participants had paid employment of >15 hours/week at any assessment (55%), physical function was also good at any assessment in the vast majority (≥90%), but satisfaction with sexuality was low with 41% indicating dissatisfaction at study entry. HIV viral load remained relatively stable during the study period.

Table S1 presents the distribution of nominated sentiments for men and women. Emotional sentiments were the most common overall, with 209 respondents nominating an emotional sentiment one or more times, 182 men and 27 women. For men and women, the distribution of the prevalence of sentiments was quite similar for emotional, interpersonal, somatic, depressogenic, and anxiety which ranged from 18.0% to 26.9% for men and 22.5% to 27.5% for women. For cognitive sentiments, the prevalence for men and women was 9.2% and 13.3%, respectively, and for positive sentiments, the prevalence was 11.7% and 6.7%, for men and women, respectively. The largest difference between men and women in prevalence was 8.5% for interpersonal sentiments, considered a trivial difference (65).

Figure 2 depicts the overlap amongst the SROs of brain health for the +BHN cohort at first assessment. The missing values were treated as not meeting the threshold on an outcome only for this illustration. Each of the four sets (HADS-A, HADS-D, MHI, PDQ) and their intersections are shown with a different colour. The summation of the numbers of people in the coloured regions (n=430), shows those meeting the threshold on one or more of the brain health outcomes. The numbers of people with the threshold level on each outcome and its overlap with other outcomes is also shown in regions with different colours. For anxiety, assessed using the HADS-A, the prevalence of scores above the threshold value (≥8) and considered to be indicative of clinically important generalized anxiety is the summation of all the numbers of people (n=334) within its respective oval. The brackets show the percentage of people meeting the threshold on any of the outcome of concern. For example, the yellow region shows the percentage (14.7%) or number of people (63/430) meeting the threshold only on the outcome for anxiety. The percentage of people meeting the threshold on all four outcomes is 16.7% (72/430) as shown in the middle of the diagram. About 68% (293/430) of people meeting the threshold on a brain health outcome also exceeded the threshold on another outcome of concern. The outer area shaded in white represents the numbers of people (U=367) who did not meet the threshold on any outcome.

Table 2 presents the results of the logistic regression linking the outcomes (occurrences of high levels of symptoms indicative of depression, anxiety and/or cognitive difficulties) to reporting of sentiments using the PGI. The numbers of people with the threshold level on each outcome is presented along with the OR associated with the nomination of each of the sentiments, first unadjusted and then adjusted for other contributors. In addition, the 95% CI is presented with the c-statistic in square brackets. Complete PGI response data were available for 797 participants but there was a different amount of missing data across the different outcomes rendering the denominator to differ by outcome. For depression, assessed using the HADS-D, the prevalence of scores above the threshold value (≥8) and considered to be indicative of clinically important depression is 23.8% (183/768) and psychological distress (52) as measured by the MHI ≤ 60 was present in 38.7%. Univariately, the sentiments associated with HADS-D are indicated with grey shading; emotional and cognitive sentiments are predictive of depression, while positive sentiments have a protective effect for depressive symptoms (OR: 0.46; 95% CI: 0.23-0.84). In fact, expression of emotional and cognitive sentiments was associated with all SROs except the B-CAM which is a PerfO.

The models adjusted for all other predictors (age, sex, education, work status, satisfaction with sexuality and physical function) of brain health outcomes included all sentiments that emerged as predictive in the univariate models. Only those sentiments that remained predictive after this adjustment are shown. Emotional sentiments predicted all SROs as did cognitive sentiments which were most strongly associated with the self-report cognitive outcome (OR: 4.78: 95%CI: 2.73-8.39); the anxiety sentiments were also specific for the anxiety outcome. Positive sentiments were protective of depressive symptoms and self-reported cognitive difficulties. The only predictor of the PerfO, B-CAM were the sentiments categorized as ‘somatic’. As this outcome is on a continuous scale, the regression coefficient is interpreted as the estimated adjusted difference in

B-CAM for those expressing somatic sentiments or not: those expressing a somatic sentiment scored on average 3.84 points lower on the B-CAM.

Tables S2, S3, S4 present the results of the logistic regression linking the outcomes for the second, third and fourth assessments to reporting of sentiments on the PGI at study entry. The numbers of people with the threshold level on each outcome at successive assessments is presented along with the OR associated with the nomination of each of the sentiments, first unadjusted and then adjusted for other predictors. The amount of missing data across different outcomes is shown for each successive assessment. Sentiments categorized as depressogenic were not predictive of any of the outcomes at study entry, but these sentiments were predictive of the emergence of anxiety symptoms (OR: 1.57: 95%CI: 1.02-2.41) and low self-reported cognitive ability (OR: 1.58: 95%CI: 0.90-2.74) on the third assessment. The c-statistics for all successive visits are estimated to be ≥ 0.70 (good to excellent prediction).

Table 3 presents the results of the GEE model linking the outcomes at any visit to reporting of sentiments on the PGI at study entry. The numbers of responses with the threshold level at any visit on each outcome is presented along with the total number of responses available for each outcome at any visit as the denominator. The OR and the 95% CI associated with the nomination of each of the sentiments is presented, first unadjusted and then adjusted for other predictors. The models adjusted for other predictors included all sentiments that emerged as predictive in the univariate models. Only those sentiments that remained predictive after this adjustment are shown. Emotional and cognitive sentiments predicted all SROs. The cognitive sentiments were most strongly associated with the SRO of cognitive ability (OR: 4.57: 95% CI: 2.96-7.07). The anxiety sentiments were specific for anxiety and the presence of psychological distress at any visit. Positive sentiments remained protective of depressive symptoms and self-reported cognitive difficulties. The only predictor of the B-CAM were somatic sentiments with those expressing such sentiments scoring on average 2.88 points lower on the B-CAM.

Table 4 presents the results of the logistic regression linking the outcomes to other predictors. The numbers of people with the threshold level of each outcome are presented unadjusted along with the OR associated with each other predictor. Univariately, the other predictors associated with the outcome are illustrated with grey shading. In addition, the 95% CI is presented along with the c-statistic in square brackets. Work status, satisfaction with sexuality and physical function predicted all outcomes while age predicted all outcomes except the SRO for cognitive ability.

5.9-Discussion

The presence of emotional and cognitive sentiments was particularly informative: in adjusted analyses, these sentiments were associated with all SROs of depression, anxiety, psychological distress and cognitive ability (HADS-D, HADS-A, MHI, PDQ/C3Q), respectively. In contrast, anxiety sentiments were only associated with the presence of anxiety as measured by the HADS-A. The GEE model which links the outcomes at any visit to reporting of sentiments on the PGI at study entry shows that anxiety sentiments were predictive of the presence or emergence of the outcomes for anxiety and psychological distress at any visit. Positive sentiments were protective against depression as measured by the HADS-D, and the presence of self-reported cognitive difficulties as measured by the PDQ/C3Q.

Scores on the B-CAM were only associated with somatic sentiments and no association with cognitive sentiments was found. Such an association may be indicative of the complex phenotypes of brain health in HIV which include both cognitive and affective components (66). Similarly, in the general older and aging population without dementia, somatic anxiety was associated with poorer cognitive performance (67). Thus, a possible association between somatic sentiments and the PerfO, B-CAM.

Emotional sentiments were also associated with all SROs when looking at the persistence of symptoms over time. The nomination of emotional sentiments on the PGI provides an early-warning system for the identification of the presence or emergence of brain health concerns including psychological distress, depression, anxiety, and cognitive difficulties. Cognitive sentiments were also associated with all SROs at study entry and at each successive assessment with the exception of HADS-A at second assessment. Cognitive sentiments had the strongest association with self-reported cognitive ability amongst all sentiment groups and outcomes. Longitudinal analyses show that the c-statistics remained relatively stable across each successive assessment strengthening the case of using the PGI as an early-warning system for identifying brain health outcomes as the sentiments nominated at study entry were also predictive at subsequent assessments (Refer to Tables S2, S3 & S4).

Our study presents a new approach to utilize the rich data available from the PGI which can be readily administered in just over 5 minutes. The nomination of 5 life-areas of concern on the PGI was predictive of the presence and emergence of all brain health outcomes considered in our analyses. Hence, clinicians can ask patients 5 life-areas of concern affecting their condition to identify areas relevant to the sentiment analysis framework to be able to use a patient-centered approach for a referral to a specialist for diagnosis. This approach can enable the clinician to identify specific brain health concerns early-on by identifying the high-risk sentiments associated with a particular outcome. Our approach eliminates the need to administer the HADS, MHI and PDQ/C3Q which require substantial attention and time from the people completing them.

None of the generic preference-based measures include all of the domains that can be identified within the PGI. The PGI and EuroQoL 5 Dimension 5 Level (EQ-5D-5L) were shown to have a moderate correlation of 0.52 (68). Among patients with Parkinson's disease, agreement between standard outcome measures and the PGI was estimated at 85-100% for walking, 69-100% for fatigue, 38-75% for depression and 20-80% for memory or concentration (69). Another study used the triangulation of both the ICF and Patient-Reported Outcomes Measurement Information System (PROMIS) framework to identify 10 core PRO domains for people affected by a chronic pain condition to include: pain interference, physical function, sleep disturbance, anxiety, depression, ability to participate in social roles and activities, fatigue, sleep-related impairments and self-efficacy (70). All of these domains and more were identifiable from the life areas nominated on the PGI in the +BHN cohort. Life areas related to other predictors of work status, satisfaction with sexuality and physical function were also identifiable within the PGI. In the absence of preference-based measures specific to people with HIV, the PGI provides information that can be used to quickly identify the presence or emergence of brain health challenges.

More recently, studies have explored decision-making under ambiguity postulating that somatic markers characterize positive or negative emotional responses (71, 72). Such responses can affect decision-making by creating physiological responses (73) which can possibly interfere with scores on PerfOs such as the B-CAM (67). Although, the C3Q and B-CAM are both measures of cognitive ability, the C3Q is a SRO which measures different response processes. PerfOs or behavioural measures are primarily developed to be used under "experimental" conditions for detecting within-person effects and so maximizing within-person reliability. SROs are most often developed to maximize between-person variability and hence mathematically their correlation is expected to be low (74). Also, error variance is increased by situational factors such as the emotional state of the person performing a task or taking a test, noise, illumination, distance from the screen, the presence of other people and so on (74). C3Q which is specific to the +BHN cohort and is a SRO which may provide more information on cognitive difficulties in people with HIV.

Our models include both cognitive and depressogenic sentiments which is unique to this study. As C3Q finalized 15 items for the behaviour and emotional domain (16), depression and anxiety may exhibit a close association with cognitive predictors for people with HIV when compared with the general population where depressogenic sentiments are more noticeable (28, 29, 75, 76). Previously, studies have shown that such sentiments with extreme polarity were associated with depression while those with low polarity were predictive of anxiety in the general population (27, 75-84).

Our study is unique as it includes a large representative longitudinal sample of aging people with HIV. Previous studies developed models to predict depression for diagnosed patients and were deficient in terms of sample size and excluded the possible comorbidity and interaction amongst several brain health outcomes. About half of the people approached for participation agreed to enter the +BHN cohort (21). The information provided by those declining to participate indicated that there was a selection bias towards including those less likely to work due to time constraints and those with more cognitive challenges (85). Thus, there is a possibility that brain health outcomes may be overestimated in our cohort when compared with the population of people with HIV across Canada.

The prevalence of depression in people with HIV has been estimated to be in the range of two to four times that of the general population (86, 87). The prevalence of mental health concerns in our cohort was estimated at 39.1%, comparable with 38.6% in an Ontario-based cohort of people with HIV (30). The prevalence of anxiety was estimated to be 44.4% which is close to the estimates obtained for people with HIV in low-income countries (45.6%), exhibiting anxiety disorder using a pooled systematic review (88). These observations mitigate the scope for a significant selection bias in the results obtained for brain health concerns in our cohort. The prevalence of symptoms associated with self-reported cognitive difficulties in our cohort was estimated to be 20.4%. A meta-analysis of the prevalence of asymptomatic neurocognitive impairment and mild neurocognitive disorder showed estimates at 23.5% (95% CI: 20.3%-26.8%) and 13.3% (95% CI:

10.6%-16.3%), respectively (89). Thus, estimates of brain health concerns for our cohort do not deviate considerably from global estimates for people with HIV.

A limitation of this study is that interpersonal sentiments were not associated with brain health outcomes in our cohort. This may be due to a difficulty in assigning partial text such as a reference to family or friends which does not have a clear polarity and could not be assigned to the negative interpersonal category. Encouraging more complete responses to the life areas nominated on the PGI for interpersonal concerns could improve the predictability of our models.

This study contributes valuable information to quickly identify serious brain health concerns early-on in the research process so that action can be taken. The results are also applicable in the clinical context where the areas nominated could be further queried for diagnostic and treatment purposes.

5.10-Conclusions

This study shows that sentiments nominated on the PGI can provide a framework that can be used as an early-warning system for the identification of brain health challenges in people with HIV. First, the PGI provides a quick and efficient means of predicting brain health concerns without the need to administer the HADS-D, HADS-A, MHI and PDQ/C3Q. Second, it ensures that people with chronic concerns are able to access the help that they need without much delay. This early-warning system via the life areas nominated on the PGI can quickly identify patient concerns relevant to brain health challenges and facilitate in the referral, diagnosis and treatment of relevant concerns. Our study takes sentiment analysis a step closer to identifying solutions that are patient-centered and easy to implement. The 5 life-areas nominated on the PGI are shown to be predictive of both the presence and emergence of self-reported brain health concerns in our cohort of people with HIV.

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Tables and figures

Figure 1: Theoretical framework of the measurement model

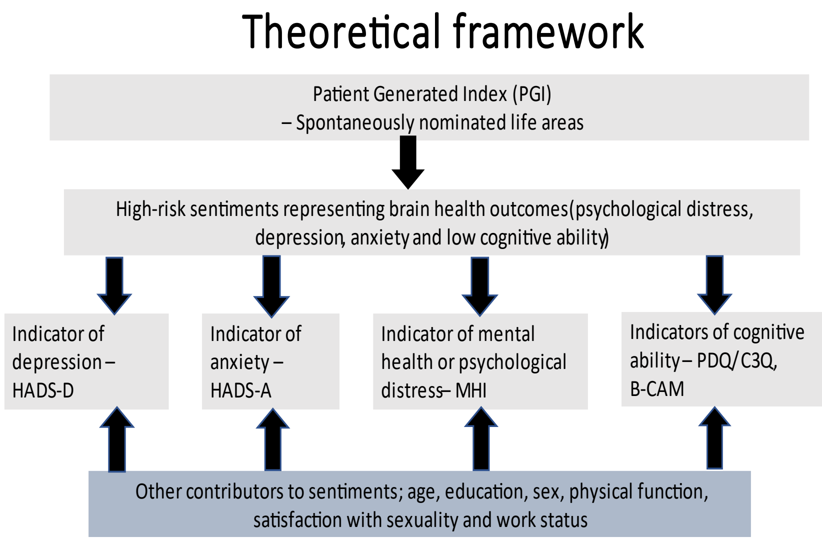


Table 1: Socio-demographic and clinical characteristics of the sample

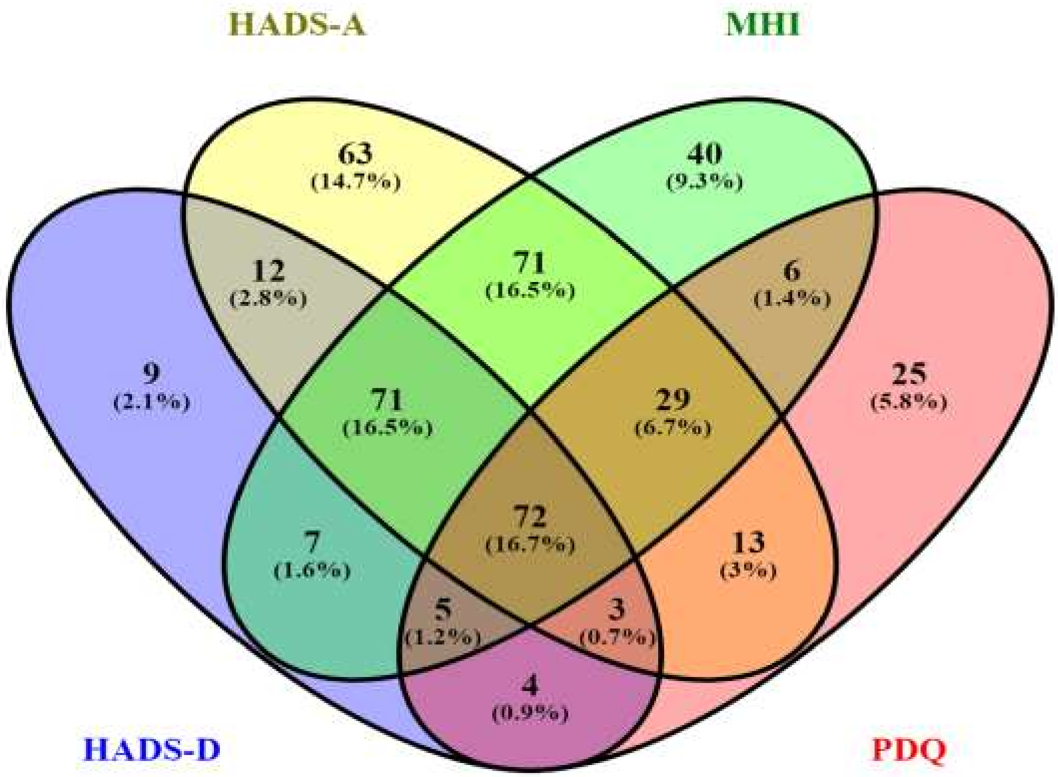
Assessment	First (study entry)	Second	Third	Fourth
	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean ± SD
Sex, male	677 (84.9%)	632 (85.1%)	613 (85.0%)	565 (85.0%)
Age, Mean ± SD	52.9 ± 8.2	54.0 ± 8.3	54.7 ± 8.1	55.4 ± 8.1
Education				
No education or only kindergarten	35 (4.5%)	28 (3.9%)	25 (3.6%)	24 (3.7%)
Primary school	209 (27.0%)	195 (26.9%)	188 (26.7%)	168 (25.8%)
High school	268 (34.6%)	255 (35.1%)	249 (35.4%)	231 (35.4%)
CEGEP/College	184 (23.8%)	173 (23.8%)	170 (24.2%)	161 (24.7%)
University	78 (10.1%)	75 (10.3%)	72 (10.2%)	68 (10.4%)
Satisfaction with sexuality				
Very dissatisfied	155 (20.1%)	126 (19.0%)	111 (18.0%)	102 (16.6%)
Dissatisfied	161 (20.9%)	148 (22.3%)	128 (20.7%)	139 (22.7%)
Neither satisfied nor dissatisfied	225 (29.2%)	191 (28.8%)	172 (27.8%)	173 (28.2%)
Satisfied	176 (22.8%)	156 (23.5%)	158 (25.6%)	142 (23.2%)
Very satisfied	55 (7.1%)	42 (6.3%)	49 (7.9%)	57 (9.3%)
Working (paid work ≥15 h/w)	364 (45.9%)	310 (45.1%)	289 (45.3%)	287 (45.3%)
Good physical function (score of ≥ 45/100)	726 (93.6%)	628 (93.6%)	577 (91.3%)	572 (91.7%)
HIV Immune Markers				
Current CD4 in cells/mm3	636.3 ± 283.2	653.1 ± 265.4	647.7 ± 277.6	657.0 ± 267.9
Nadir CD4 in cells/mm3	218.0 ± 171.4	215.8 ± 166.9	213.4 ± 163.9	211.5 ± 162.0
HIV viral load (VL), undetectable (VL≤50 copies/mL)	710 (92.2%)	627 (95.3%)	598 (94.3%)	557 (93.3%)
Years since HIV diagnosis	16.8 ± 7.9	17.6 ± 7.9	18.5 ± 7.9	19.3 ± 7.9

Figure 2: Overlap of brain health outcomes for the +BHN cohort

Venn diagram

(VENNY 2.1, Oliveros 2015)

U = 367



HADS-D: Hospital Anxiety and Depression subscale for depression

HADS-A: Hospital Anxiety and Depression subscale for anxiety

MHI: Mental Health Index of the RAND-36

PDQ: Perceived Deficits Questionnaire

Table 2: First assessment cross-sectional unadjusted and adjusted sentiment analysis

	HADS-D (183/768)	**HADS-A (334/759)**	**MHI (301/778)**	**PDQ/C3Q (157/779)**	**B-CAM (n=731)**
	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	b (se) [t]
Unadjusted					
Emotional	2.04 (1.42-2.92) [0.596]	1.86 (1.34-2.59) [0.607]	1.94 (1.40-2.69) [0.580]	2.15 (1.47-3.13) [0.638]	-0.99 (1.19) [-0.84]
Interpersonal	1.05 (0.67-1.62) [0.546]	1.09 (0.75-1.60) [0.579]	1.20 (0.82-1.75) [0.535]	0.78 (0.48-1.23) [0.597]	-0.08 (1.44) [-0.06]
Somatic	1.12 (0.73-1.70) [0.549]	1.11 (0.76-1.62) [0.579]	1.04 (0.71-1.52) [0.538]	1.30 (0.84-2.00) [0.599]	-3.84 (1.38) [-2.78]
Depressogenic schemata	1.06 (0.71-1.57) [0.550]	1.10 (0.77-1.56) [0.578]	1.07 (0.76-1.52) [0.537]	0.94 (0.60-1.44) [0.592]	1.20 (1.27) [0.95]
Anxiety	1.20 (0.78-1.82) [0.550]	1.44 (0.99-2.10) [0.585]	1.32 (0.91-1.91) [0.549]	1.15 (0.73-1.80) [0.597]	-0.26 (1.36) [-0.19]
Cognitive	1.77 (1.05-2.93) [0.554]	1.86 (1.12-3.13) [0.590]	1.67 (1.03-2.71) [0.554]	4.56 (2.76-7.55) [0.639]	-2.54 (1.79) [-1.42]
Positive	0.46 (0.23-0.84) [0.582]	0.79 (0.49-1.27) [0.578]	0.77 (0.47-1.24) [0.533]	0.36 (0.16-0.72) [0.619]	-1.19 (1.83) [-0.65]
Adjusted: Sentiments + Other predictors					
Emotional	1.98 (1.34-2.94) [0.749]	1.68 (1.17-2.42) [0.740]	1.79 (1.26-2.57) [0.733]	1.97 (1.31-2.95) [0.736]	
Interpersonal					
Somatic					-3.04 (1.29) [-2.36]
Depressogenic schemata					
Anxiety		1.72 (1.14-2.62) [0.740]			
Cognitive	1.61 (0.90-2.85) [0.741]	1.62 (0.93-2.86) [0.735]	1.50 (0.88-2.57) [0.729]	4.78 (2.73-8.39) [0.745]	
Positive	0.48 (0.23-0.93) [0.741]			0.36 (0.16-0.74) [0.737]	

All models were adjusted for the important sentiments, centre and all other predictors (age, sex, education, work status, satisfaction with sexuality, physical function)
Univariately, the sentiments associated with the threshold value are illustrated with grey shading

Table 3: First assessment at study entry to any assessment unadjusted and adjusted sentiment analysis

	HADS-D (628/2669)	HADS-A (1121/2661)	MHI (1004/2692)	PDQ/C3Q (328/1957)	B-CAM (n=2635)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	b (s.e) [z]
Unadjusted					
Emotional	1.91 (1.43-2.55)	1.85 (1.41-2.42)	1.78 (1.36-2.32)	2.10 (1.51-2.93)	-0.45 (1.03) [-0.44]
Interpersonal	1.26 (0.88-1.82)	1.04 (0.76-1.43)	1.27 (0.92-1.75)	0.83 (0.56-1.24)	-0.56 (1.18) [-0.47]
Somatic	1.21 (0.86-1.71)	1.07 (0.78-1.46)	1.16 (0.84-1.59)	1.28 (0.88-1.87)	-2.88 (1.29) [-2.23]
Depressogenic schemata	1.15 (0.83-1.60)	1.18 (0.89-1.58)	1.05 (0.78-1.41)	1.13 (0.77-1.66)	-0.79 (1.03) [0.76]
Anxiety	1.28 (0.92-1.79)	1.39 (1.02-1.89)	1.39 (1.03-1.89)	1.02 (0.69-1.53)	-0.12 (1.14) [-0.11]
Cognitive	1.77 (1.15-2.73)	1.70 (1.12-2.56)	1.80 (1.22-2.66)	4.57 (2.96-7.07)	-1.33 (1.78) [-0.75]
Positive	0.49 (0.30-0.80)	1.01 (0.68-1.51)	0.81 (0.53-1.24)	0.37 (0.20-0.68)	0.05 (1.66) [0.03]
Adjusted: Sentiments + Other predictors					
Emotional	1.83 (1.37-2.45)	1.77 (1.34-2.35)	1.61 (1.22-2.13)	2.00 (1.41-2.82)	
Interpersonal					
Somatic					-2.21 (1.18) [-1.87]
Depressogenic schemata					
Anxiety		1.65 (1.20-2.26)	1.52 (1.12-2.06)		
Cognitive	1.69 (1.10-2.61)	1.39 (0.92-2.11)	1.61 (1.08-2.40)	4.78 (3.10-7.39)	
Positive	0.55 (0.33-0.91)			0.36 (0.19-0.67)	

All models were adjusted for the important sentiments, centre and all other predictors (age, sex, education, work status, satisfaction with sexuality, physical function)

Univariately, the sentiments associated with the threshold value are illustrated with grey shading

Table 4: Univariate analysis of other predictors to sentiments at study entry

	HADS-D (183/768)	**HADS-A (334/759)**	**MHI (301/778)**	**PDQ/C3Q (157/779)**	**B-CAM (n=731)**
Univariate	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	b (se) [t]
Age	0.97 (0.95-0.99) [0.594]	0.96 (0.94-0.98) [0.619]	0.97 (0.95-0.99) [0.583]	0.98 (0.96-1.00) [0.606]	-0.39 (0.06) [-6.11]
Sex	1.56 (1.00-2.41) [0.560]	0.83 (0.55-1.26) [0.578]	0.92 (0.61-1.38) [0.539]	1.30 (0.80-2.05) [0.600]	-7.40 (1.45) [-5.09]
Education	0.21 (0.08-0.54) [0.602]	0.49 (0.21-1.16) [0.602]	0.44 (0.19-1.00) [0.562]	0.44 (0.16-1.19) [0.609]	11.36 (2.98) [3.81]
Work status	2.02 (1.43-2.89) [0.606]	1.61 (1.20-2.18) [0.597]	1.52 (1.13-2.05) [0.567]	2.91 (1.97-4.39) [0.665]	-7.46 (1.04) [-7.18]
Satisfaction with sexuality	0.10 (0.03-0.27) [0.683]	0.16 (0.08-0.31) [0.687]	0.16 (0.07-0.32) [0.687]	0.48 (0.21-1.00) [0.655]	5.43 (2.34) [2.32]
Physical function	2.34 (1.26-4.27) [0.570]	1.44 (0.79-2.63) [0.582]	2.31 (1.28-4.23) [0.552]	2.96 (1.60-5.40) [0.622]	-7.75 (2.17) [-3.58]

All shaded other predictors (older age, female, more education, adequate employment, satisfaction with sexulaity and better physical function) were significantly associated with brain health outcomes

Univariately, the other predictors associated with the threshold value are illustrated with grey shading

Supplement

Table S1: Distribution of sentiments nominated on the PGI by sex

	Men (n=677)		Women (n=120)	
	No.	**Percent**	**No.**	**Percent**
Emotional	182	26.9	27	22.5
Interpersonal	123	18.2	32	26.7
Somatic	124	18.3	29	24.2
Depressogenic	145	21.4	33	27.5
Anxiety	122	18.0	27	22.5
Cognitive	62	9.2	16	13.3
Positive	79	11.7	8	6.7

Table S2: First assessment to second assessment unadjusted and adjusted sentiment analysis

	HADS-D (143/655)	HADS-A (272/665)	MHI (254/668)	PDQ/C3Q (23/154)	B-CAM (n=674)
	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	b (se) [t]
Unadjusted					
Emotional	1.69 (1.12-2.52) [0.628]	2.05 (1.45-2.91) [0.598]	1.56 (1.10-2.21) [0.576]	3.43 (1.35-8.88) [0.699]	0.23 (1.24) [0.18]
Interpersonal	1.54 (0.95-2.45) [0.620]	0.91 (0.60-1.39) [0.543]	1.42 (0.93-2.15) [0.565]	0.58 (0.15-1.86) [0.629]	-0.08 (1.50) [-0.05]
Somatic	1.36 (0.84-2.16) [0.605]	1.09 (0.72-1.65) [0.543]	1.23 (0.81-1.86) [0.556]	1.20 (0.35-3.60) [0.613]	-1.88 (1.47) [-1.28]
Depressogenic schemata	1.35 (0.86-2.08) [0.605]	0.99 (0.68-1.44) [0.543]	1.11 (0.76-1.61) [0.556]	1.30 (0.41-3.71) [0.627]	0.71 (1.31) [0.54]
Anxiety	1.41 (0.88-2.23) [0.609]	2.01 (1.35-2.99) [0.579]	1.59 (1.07-2.36) [0.574]	0.50 (0.11-1.64) [0.632]	0.29 (1.42) [0.21]
Cognitive	2.04 (1.15-3.57) [0.616]	1.62 (0.95-2.75) [0.551]	2.25 (1.33-3.87) [0.573]	5.24 (1.35-19.82) [0.641]	-1.53 (1.92) [-0.80]
Positive	0.56 (0.26-1.10) [0.619]	1.45 (0.87-2.43) [0.552]	0.66 (0.37-1.13) [0.559]	0.00 (0.00-0.52) [0.669]	1.10 (1.84) [0.59]
Adjusted: Sentiments + Other predictors					
Emotional	1.51 (0.96-2.37) [0.772]	1.97 (1.34-2.89) [0.730]	1.44 (0.97-2.13) [0.753]	4.10 (1.26-14.60) [0.836]	
Interpersonal					
Somatic					
Depressogenic schemata					
Anxiety		2.86 (1.84-4.47) [0.741]	2.05 (1.31-3.22) [0.758]		
Cognitive	2.14 (1.12-4.06) [0.775]		1.86 (1.02-3.42) [0.755]	5.99 (1.16-30.91) [0.853]	
Positive					

All models were adjusted for the important sentiments, centre and all other predictors (age, sex, education, work status, satisfaction with sexuality, physical function)

Univariately, the sentiments associated with the threshold value are illustrated with grey shading

Table S3: First assessment sentiments to third assessment unadjusted and adjusted sentiment analysis

	HADS-D (152/622)	HADS-A (261/621)	MHI (234/627)	PDQ/C3Q (69/440)	B-CAM (n=631)
	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	b (se) [t]
Unadjusted					
Emotional	1.65 (1.11-2.45) [0.588]	1.72 (1.20-2.46) [0.581]	1.48 (1.03-2.12) [0.567]	1.82 (1.04-3.14) [0.615]	0.16 (1.24) [0.13]
Interpersonal	1.89 (1.18-2.99) [0.586]	0.96 (0.62-1.48) [0.556]	1.20 (0.77-1.86) [0.557]	1.14 (0.58-2.17) [0.590]	-0.69 (1.51) [-0.46]
Somatic	1.20 (0.75-1.91) [0.565]	1.19 (0.78-1.82) [0.557]	1.38 (0.90-2.11) [0.569]	1.20 (0.61-2.28) [0.597]	-3.14 (1.49) [-2.11]
Depressogenic schemata	1.38 (0.89-2.11) [0.568]	1.24 (0.85-1.82) [0.560]	1.00 (0.68-1.48) [0.547]	1.09 (0.56-2.01) [0.592]	0.10 (1.32) [0.07]
Anxiety	1.36 (0.86-2.13) [0.560]	1.49 (0.99-2.24) [0.570]	1.43 (0.95-2.14) [0.567]	1.01 (0.52-1.88) [0.591]	-0.24 (1.40) [-0.17]
Cognitive	2.02 (1.13-3.55) [0.585]	2.27 (1.30-4.02) [0.577]	1.86 (1.07-3.22) [0.573]	4.81 (2.25-10.23) [0.654]	-1.36 (1.87) [-0.72]
Positive	0.70 (0.35-1.32) [0.563]	1.01 (0.59-1.72) [0.556]	1.14 (0.66-1.95) [0.552]	0.28 (0.06-0.83) [0.617]	1.31 (1.86) [0.70]
Adjusted: Sentiments + Other predictors					
Emotional	1.81 (1.15-2.84) [0.775]	1.76 (1.18-2.62) [0.737]	1.47 (0.98-2.19) [0.735]	1.97 (1.08-3.54) [0.689]	
Interpersonal	1.89 (1.10-3.25) [0.776]				
Somatic					-2.09 (1.41) [-1.48]
Depressogenic schemata					
Anxiety		1.56 (0.98-2.46) [0.733]			
Cognitive	2.09 (1.07-4.04) [0.774]	2.29 (1.23-4.32) [0.737]	1.78 (0.97-3.27) [0.736]	6.61 (2.90-15.26) [0.728]	
Positive				0.26 (0.06-0.81) [0.697]	

All models were adjusted for the important sentiments, centre and all other predictors (age, sex, education, work status, satisfaction with sexuality, physical function)

Univariately, the sentiments associated with the threshold value are illustrated with grey shading

Table S4: First assessment sentiments to fourth assessment unadjusted and adjusted sentiment analysis

	HADS-D (150/614)	HADS-A (254/616)	MHI (215/619)	PDQ/C3Q (97/588)	B-CAM (n=599)
	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	OR (95% CI) [c]	b (se) [t]
Unadjusted					
Emotional	1.94 (1.30-2.89) [0.589]	1.89 (1.31-2.72) [0.588]	1.85 (1.28-2.67) [0.582]	2.15 (1.35-3.40) [0.623]	-0.38 (1.25) [-0.31]
Interpersonal	1.32 (0.82-2.11) [0.566]	1.07 (0.69-1.63) [0.547]	1.32 (0.85-2.05) [0.557]	0.86 (0.47-1.50) [0.580]	-0.60 (1.49) [-0.40]
Somatic	1.21 (0.75-1.92) [0.563]	0.88 (0.57-1.34) [0.553]	1.09 (0.71-1.66) [0.552]	1.30 (0.75-2.21) [0.584]	-2.00 (1.46) [-1.37]
Depressogenic schemata	1.13 (0.72-1.74) [0.557]	1.53 (1.04-2.25) [0.565]	1.06 (0.71-1.57) [0.547]	1.67 (0.99-2.74) [0.597]	-0.55 (1.30) [-0.42]
Anxiety	1.30 (0.82-2.03) [0.561]	1.13 (0.75-1.69) [0.550]	1.40 (0.93-2.11) [0.563]	0.83 (0.45-1.44) [0.582]	-1.06 (1.38) [-0.76]
Cognitive	1.92 (1.09-3.33) [0.564]	1.77 (1.04-3.04) [0.558]	1.88 (1.10-3.22) [0.568]	5.42 (2.99-9.84) [0.648]	0.98 (1.87) [0.52]
Positive	0.42 (0.18-0.84) [0.580]	1.21 (0.71-2.05) [0.548]	0.91 (0.51-1.57) [0.548]	0.41 (0.15-0.92) [0.602]	-0.46 (1.91) [-0.24]
Adjusted: Sentiments + Other predictors					
Emotional	1.92 (1.22-3.03) [0.747]	1.94 (1.29-2.92) [0.727]	1.75 (1.14-2.67) [0.752]	2.02 (1.21-3.33) [0.731]	
Interpersonal					
Somatic					
Depressogenic schemata		1.57 (1.02-2.41) [0.717]		1.58 (0.90-2.74) [0.711]	
Anxiety					
Cognitive	1.72 (0.89-3.27) [0.743]	1.29 (0.71-2.35) [0.715]	1.53 (0.82-2.83) [0.747]	5.48 (2.81-10.78) [0.746]	
Positive	0.38 (0.16-0.83) [0.746]			0.37 (0.13-0.90) [0.718]	

All models were adjusted for the important sentiments, centre and all other predictors (age, sex, education, work status, satisfaction with sexuality, physical function)

Univariately, the sentiments associated with the threshold value are illustrated with grey shading

CHAPTER6 : MANUSCRIPT 2

The Patient Generated Index (PGI) as an early-warning signal for predicting brain health concerns in people living with Human Immunodeficiency Virus (HIV):

Decision tree modeling of sentiments.

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Abstract

Background: Aging with HIV has important consequences for brain health arising from neurobiological factors associated with the illness and the antiretroviral therapy (ART) as well as from psychosocial factors related to social stigma and social interaction. To identify areas of brain health concern early-on, tree models have been utilized along with other methods associated with emotion detection and sentiment analysis.

Objective: The purpose of this study is to estimate for a cohort of people aging with HIV the life areas on the Patient Generated Index (PGI) that define people with a greater prevalence of brain health concerns including psychological distress, depression, anxiety, and cognitive impairment.

Design: The data comes from participants enrolled in the Positive Brain Health Now (+BHN) cohort (n=856). The nominated areas were category coded to a sentiment framework. A cross-sectional design was used to link self-nominated sentiments to the presence of brain health challenges as assessed using standardized measures of such constructs.

Methods: A classification and regression tree (CaRT) model was applied to identify the sentiments that contributed to people having a greater prevalence of each brain health outcome. The CaRT model was used to detect the associations and pathways that lead to a greater prevalence of the symptoms associated with these outcomes. A standardized difference of 10% was used to identify the pathways associated with a greater prevalence of the threshold value.

Results: In our cohort, the overall prevalence of symptom probability was 39.1% for psychological distress, 24.1% for clinically important depression, 44.4% for clinically important generalized anxiety and 20.1% for cognitive impairment. The CaRT model showed two pathways each for psychological distress, depression, anxiety, and three pathways for cognitive difficulties.

Cognitive sentiments were the most discriminatory for self-reported cognitive ability followed by work status, emotional, somatic and anxiety sentiments. The prevalence of self-reported cognitive difficulties for people nominating cognitive sentiments was 50.7%, when not working (defined as <15 hours/week of paid employment) and also nominating additional emotional sentiments, the prevalence rate was 82.4%. Emotional sentiments were the most discriminatory for both psychological distress and anxiety. Work status was the most discriminatory for clinically

important depression followed by cognitive sentiments and physical function. Positive sentiments were protective of cognitive function and depressive symptoms.

Conclusions: Cognitive and emotional sentiments along with work status were the most discriminatory variables for identifying brain health concerns. The category coded sentiment framework identified the high-risk sentiments associated with a greater prevalence of brain health outcomes.

6.1-Introduction

By the end of 2020, there were an estimated 37.7 million people living with HIV (1), with about 65,811 in Canada (2-4). While there is no cure, the HIV infection has become a manageable chronic health condition. As a result, there is now a substantial population of people aging with HIV. Aging with HIV has important consequences for brain health arising from neurobiological factors associated with the illness and the antiretroviral therapy (ART) as well as from psychosocial factors related to stigma and social interaction (5-9).

High rates of conditions associated with mood and cognition have been reported among people with HIV, and these substantially lower quality of life (QOL); these concerns include psychological distress, anxiety, depression, and cognitive difficulties. Quick identification of these concerns is desirable in the clinic setting as targeted interventions may improve QOL.

The Patient Generated Index (PGI) (10) is a personalized measure of QOL. It asks people to spontaneously nominate areas of life related to their condition that affect their QOL. These areas, expressed in free text, are then rated on severity and importance. This measure takes under 5 minutes to complete and can easily be done in the clinic or research setting to provide a measure of QOL. In addition, text threads are then available for analysis using several frameworks and related lexicons. For example, in the recent work by the Positive Brain Health Now (+BHN) team, the life areas nominated on the PGI were mapped to the World Health Organization's International Classification of Functioning, Disability and Health (ICF) to identify areas of disability that most impacted QOL (11-18). In this regard, the PGI can simultaneously provide both semi-qualitative and quantitative information.

Here, we use a 'semi-qualitative' approach to identify the areas nominated on the PGI that are associated with a greater prevalence of brain health concerns. To this end, we selected the framework of sentiment analysis to code the text threads. Sentiments are attitudes, thoughts, or judgments prompted by feelings (19) or general feelings about a situation (19, 20). We considered that this framework was best suited to identify mental health disorders from text threads on the PGI because many of the areas related to brain health concerns were "invisible".

Sentiment analysis or opinion mining is the automatic processing of sentiments, opinions, and subjectivity within textual data (21). Tree models which are increasingly popular due to their ease of understanding for sentiment analysis (22, 23). Decision trees recently demonstrated the highest accuracy across several machine learning experiments for detecting depression using textual data of social media users (24). In healthcare settings, decision trees had an excellent prediction (>80% agreement) among those derived from quantitative ratings of care and textual analysis (25). A decision tree starts with a decision node which then shows multiple pathways for potential decisions and/or outcomes. The decision tree can be used as a pathway for the clinician to address patient categories and aspects of assessment for brain health outcomes. We use decision trees to identify the pathways that are associated with a greater prevalence of brain health concerns in people with HIV.

Thus, the purpose of this study is to estimate for a cohort of aging people with HIV the extent to which a self-nomination of areas on the PGI is associated with a greater prevalence of brain health concerns of psychological distress, depression, anxiety, and cognitive impairment.

6.2-Methods

Data for this study came from the initial visit of the +BHN cohort (n=856). This cohort has been well described previously (16, 17, 26, 27). Briefly, cohort members were recruited between 2014 and 2016 from five Canadian sites. Participants were over 35 years of age at time of enrolment, able to communicate in either English or French, living with HIV for at least one year, and without dementia, co-morbidity affecting cognition, substance abuse, or life-threatening illnesses.

All participants for whom the respective exposure and outcome data were available were included in the analyses. Cross-sectional exposure data collected at study entry included the areas of concern nominated on the PGI as well as other exposure and outcome measures.

6.3-Measurement

The exposure was measured by category coding the text threads representing the nominated areas on the PGI. The PGI is an individualized measure developed to assess the impact of a health condition on QOL (10). PGI consists of three steps: (1) nomination of the top five areas of life affected by the health condition, entered as free text; (2) rating the severity of these five areas plus a sixth area for all other aspects affecting QOL using a scale from 0 to 10, where 0 is as bad as possible and 10 is as good as possible; and (3) distribution of 12 tokens among all 6 nominated areas based on the importance for improvement, with more tokens spent on areas that the participant would most want to see improved. A global index score is calculated by multiplying the severity score (step 2) by the number of tokens allocated to that area and summing over the six areas, where 0 is poorest possible QOL and 100 represents best QOL. The +BHN team has published extensively on the PGI including preliminary data on the cohort (28). In this study, only the text threads were analysed.

6.4-Outcome measures

The outcome measures were obtained using standard questionnaires and were dichotomized at known cut-points. Three patient-reported outcome measures were used as indicators of brain health disorders: psychological distress, depression, anxiety, and cognitive impairment.

The Mental Health Index (MHI) of the RAND-36 (29) was used to identify people who are likely to experience psychological distress (30), with a score lower than 60 indicative of distress (31). The Hospital Anxiety and Depression Scale (HADS) consists of seven items for anxiety (HADS-A) and seven items for depression (HADS-D). These were used to identify people who are likely to have clinical depression or generalized anxiety. Scores on the sub-scales range from 0 to 21, with a score ≥ 8 indicative of clinically important depression or generalized anxiety (32, 33).

Cognitive impairment was assessed using the Perceived Deficits Questionnaire (PDQ), a self-report outcome (SRO) developed for use in people with Multiple Sclerosis (MS) that assesses the domains of retrospective memory, prospective memory, attention or concentration, and planning or organization (12). The PDQ comprises 20 items scored on a 5-point ordinal scale (0 to 4) yielding values ranging for 0 to 80, with 40 or more indicating cognitive impairment (12).

6.5-Other predictors

Known predictors of brain health outcomes in HIV include age, sex, education, physical function, satisfaction with sexuality, and work status (34-39). Physical function was assessed on a binary scale with a score of <45/100 on the Physical Function Index (PFI) of the RAND-36 representing poor physical function (40). Work status is measured on a binary scale with individuals categorized as working when paid employment is at least 15 hours/week (41). Sex is categorized as binary with '0' for male and '1' for female. Age was measured on a continuous scale with a 1-year interval. Education is measured on a categorical scale from 1 to 5 with '1' representing little or no education and '5' being university graduation. Satisfaction with sexuality is measured by a single question drawn from the WHOQOL-HIV-BREF, scored from 1 to 5 (42).

6.6-Statistical analysis

6.6.1-Category coding to sentiments

Emotion detection is the means to identify distinct human emotion types, while sentiment analysis is associated with the detection of polarity (i.e., negative, positive, neutral) (43, 44). Negative sentiments can be either explicit or deliberately formed using key words or implicit and involuntarily formed at the unconscious level and detected through human judgment (45). Tokenization is often used for sentiment analysis with the objective of separating a piece of text into smaller units often known as tokens (46). We used tokenization to identify the sentiments nominated by the +BHN cohort on Step 1 of the PGI at study entry, this process marked the sentiments as distinct from unrelated text. Sentiments were extracted and tokenized (a process also referred to as sentiment annotation) using the lexicon identified from the literature (24, 47, 48) and by applying the semantic representations identified through high-level human judgment which is often used as a "gold standard" for supervised machine learning experiments (49-52). Negative sentiments were assigned to one of the six categories identified from the literature: emotional, interpersonal, somatic, depressogenic schemata, anxiety, or cognitive categories (Refer to Table 1). Since the PGI prompts respondents to nominate areas that impact their QOL, there is a tendency to nominate negative sentiments. Nevertheless, some participants also expressed positive sentiments which were assigned to a single category referred to as 'positive'. These categories were then dichotomized and classified as '1' when a sentiment was nominated one or more times, and '0' when a sentiment was not nominated.

6.6.2-Statistical model

Classification and Regression Tree (CaRT) is a non-parametric tree model, useful for explaining a continuous or categorical outcome in terms of multiple exposures or explanatory variables. CaRT is a supervised hierarchical clustering tree model and provides a systematic approach that uses both classification and regression of data (24). This hierarchical classification predicts group members by recursively or sequentially splitting the data into dichotomous groups that contain increasingly similar responses for the outcome. The model applies statistical methods such as data mining to identify the crucial associations and pathways that lead to a greater prevalence of the outcome associated with binary concerns (53). CaRT is often used for estimating health and well-being using sentiment analysis (44). This model is frequently used to make categorizations or prediction algorithms on a target outcome (54-56).

As the CaRT is a non-linear analytical tool (57), it was appropriate for our study because the outcome measures were not normally distributed and were continuous but dichotomized as known cut-points. In our models, the CaRT classifies individuals based on an analysis of the categorized sentiment groups for each outcome measure of brain health. Every tree starts with a "root node" which splits into two "decision nodes" based on the value of an independent predictor variable (a sentiment category or another predictor in our models). The resulting decision node consists of a subset of observations that may be further split in accordance with the partitioning criterion/criteria until those are no longer met, resulting in terminal nodes which by definition cannot be split any further. A complete partition of the observations in the root node is represented with the collection of terminal nodes of a decision tree. For our CaRT models, the criterion for determining the terminal nodes was based on the deterministic prevalence of each outcome measure. For example, the deterministic prevalence of clinically important depression as measured using the HADS-D in the +BHN cohort is 24.1%. Thus, the terminal node is set at a point when the minimum observations is above the 10% threshold of (183/759), or 19 observations.

Our focus was to identify the pathways associated with the sentiment categories identified from the literature and coded using the sentiment analysis framework. Other binary contributors of work status, physical function and sex were also classified. As the representation of a CaRT model is a binary tree, a limitation was that non-binary other predictors of age, education and satisfaction with sexuality were not classified. Data were analysed using the SAS (previously "Statistical Analysis System") version 9.4.

6.7-Results and analyses

6.7.1-Description of the sample

Data were available from 797 people who provided complete responses and assigned a total of 12-points to the life-areas nominated at study entry on the PGI. Table 2 describes the socio-demographic and clinical characteristics at study entry. The numbers of people and their composition in the +BHN cohort is shown as percentages in brackets. The mean levels of the HIV immune markers for the cohort are presented along with their standard deviations. At study entry, the cohort was composed mostly of adult men with a mean age of 52.9 years. Almost all participants had a high school education or more. Over half of the participants had paid employment of >15 hours/week at any assessment (55%), physical function was also good at any assessment in the vast majority (≥90%), but satisfaction with sexuality was low with 41% indicating dissatisfaction at study entry.

6.7.2-Results

Distribution analysis of nominated sentiments for men and women showed a trivial difference in our cohort. Thus, the analyses combined men and women while including sex as a contributor within the tree models.

Figure 1 shows how the prevalence of psychological distress varied according to the nomination of sentiments on the PGI. Complete PGI response data were available for 797 participants but there was a different amount of missing data across the different outcomes. For the MHI of the RAND-36, complete data for the outcome and other predictors (work status, physical function, and sex) were available for 769 people. The CaRT model showed that emotional sentiments were the most discriminatory for psychological distress followed by interpersonal sentiments, work status and depressogenic sentiments. Psychological distress (58) as measured by the MHI ≤ 60 was present in 39.1% of the people. A standardized difference of 10% was used to identify the pathways that lead to greater prevalence for each respective brain health outcome (the terminal nodes meeting or exceeding this criterion were shaded in red).

The prevalence rate of psychological distress for people nominating emotional sentiments was 50.7%, with additional nomination of interpersonal sentiments the prevalence rate was 55.9%. For people not nominating emotional sentiments, not working and additionally nominating depressogenic sentiments the prevalence rate was 50.0%. Table 3-a shows the 6 variables including work status and 5 sentiment categories that contributed to the full tree for psychological distress along with their relative importance and prevalence in the whole sample. The red coloured boxes represent the presence of a variable in the pathway and the green coloured box represents the absence of a variable.

Figure 2 shows how the prevalence of depressive symptoms differed according to the nomination of the sentiments. Work status was the most discriminatory variable followed by cognitive sentiments, positive sentiments, and physical function. For depression, assessed using the HADS-D, the prevalence of scores above the threshold value (≥8) and considered to be indicative of clinically important depression is 24.1%. The pathways that lead to a greater prevalence are shown with the terminal nodes shaded in red while those protective of depressive symptoms are shown in blue (both using a standardized difference of 10%).

Table 3-b shows the 10 variables including the other predictors of work status, physical function, sex, and the 7 sentiment categories that contributed to the full tree for clinically important depression along with their relative importance and prevalence in the whole sample. People having work problems and nominating cognitive sentiments had a prevalence rate of 48.8% (almost double that of the overall prevalence rate). For those not working, not nominating cognitive sentiments, nominating positive sentiments was protective of depressive symptoms with a prevalence rate of the threshold value indicative of clinically important depression was 11.1% (less than half that of the overall prevalence rate). For those not nominating cognitive and positive sentiments, work problems may be linked to poor physical function with the prevalence rate of clinically important depression increasing to 47.0%.

Figure 3 shows how the prevalence of anxiety symptoms varied according to the nomination of sentiments. Emotional sentiments were the most discriminatory followed by work status and depressogenic sentiments. For anxiety, assessed using the HADS-A, the prevalence of scores above the threshold value (≥8) and considered to be indicative of clinically important generalized anxiety was 44.4% (highest amongst all SROs). The prevalence for people nominating emotional sentiments increased to 55.0%. For people not nominating emotional sentiments, not working and nominating depressogenic sentiments the prevalence rate was 56.1%. Table 3-c shows the 6 variables including work status and the 5 sentiment categories that contributed to the full tree for clinically important generalized anxiety along with their relative importance and prevalence in our cohort.

Figure 4 shows how the prevalence of cognitive impairment differed according to the nomination of the sentiments. Cognitive sentiments were the most discriminatory for cognitive difficulties followed by work status and sentiment categories for emotional, somatic and anxiety. For cognitive impairment, assessed using the PDQ, the prevalence of scores above the threshold value (40/80) was 20.4%. The prevalence of cognitive difficulties in people nominating cognitive sentiments was 50.7%, and for those not working and additionally nominating emotional sentiments the prevalence rate was 82.4%. The pathways that lead to greater prevalence for cognitive difficulties are shown with the terminal nodes shaded red while those that led to lower prevalence are shaded in blue. Positive sentiments were protective of cognitive function.

Table 3-d shows the 9 variables including the other predictors of work status, sex, and the 7 sentiments that contributed to the full tree for cognitive impairment with their relative importance and prevalence in the whole sample. Among all of the SROs considered, the highest prevalence rate of 82.4% was estimated for cognitive difficulties. The misclassification rate was 18.1% and discriminatory capacity (area under the receiver operating characteristics curve) (AUROC) was 0.76, considered acceptable to good.

6.8-Discussion

In our cohort, about half of the people nominating emotional sentiments meet the threshold for psychological distress. Emotional sentiments (i.e., burden, depressed mood, suicidal thoughts) were associated with a persons mood, feelings and opinions which were closely related to the emotion detection questions on the MHI. These methods are theoretically analogous and possibly contributed to the good discriminatory capacity of emotional sentiments when predicting psychological distress.

The nomination of emotional and additional interpersonal sentiments was associated with a greater prevalence of psychological distress. People not nominating emotional sentiments, working less than 15 hours/week (classified as not working), and nominating additional depressogenic sentiments had a prevalence rate of 50.0%. As depressogenic schemata are cognitive predictors of anxiety and depression, the depressogenic sentiments may be associated with difficulty in seeking or sustaining stable employment (59, 60). Also, disturbances in emotional regulation are often observed in people with somatic symptoms (61, 62).

Brain health concerns of psychological distress, depression, anxiety, and cognitive impairment are not mutually exclusive. People with depression tend to have a higher likelihood of experiencing comorbid anxiety (63) with an estimated comorbidity in the general population of 19.0% (64). Comorbidity of depression and anxiety is more common in populations with chronic concerns such in people with HIV (65). The pooled prevalence of depression in people with HIV in China was much higher at 50.8% (95% CI: 46.0-55.5%), with stigma playing a major role (7).

The overall prevalence of depression in our cohort was estimated at 24.1%, which is consistent with the estimates in other adult HIV populations. More recent estimates include a lifetime prevalence of 20.6% in a national survey of adults in the United States (66). In our cohort, work status is the most important deterministic variable followed by cognitive sentiments and poor physical function. Positive sentiments were protective of depressive symptoms and cognitive function. A meta-analysis found that despite the psychological resilience demonstrated in people with HIV these individuals were twice as likely to experience depression compared with HIV-negative individuals (67). The odds of 12-month major depressive disorder were lower in men (OR, 0.5; 95% CI: 0.46-0.55), and higher in young adults aged 18-29 years (OR, 3.0; 95% CI: 2.48-3.55), those with incomes up to USD 19,999 (OR, 1.7; 95% CI: 1.49-2.04) and in white adults (66, 68).

A meta-analysis estimated the global prevalence of HIV-associated neurocognitive disorder (HAND) at 42.6%. As the +BHN cohort excluded people with dementia, co-morbidity affecting cognition, substance abuse, or life-threatening illnesses the prevalence of cognitive impairment was 20.4%. The prevalence of low cognitive ability in our cohort was close to the estimates for asymptomatic neurocognitive impairment at 23.5% (95% CI: 20.3%-26.8%). The CaRT model showed a fourfold (82.4%) increase in prevalence for people nominating both cognitive and emotional sentiments. Symptoms such as memory problems and forgetfulness were associated with mood-related conditions such as depression in the absence of neurological degeneration (69, 70). Thus, people nominating cognitive sentiments and especially nominating additional emotional sentiments may be referred to the clinician for further assessment and possibly be treated for depression in the absence of neurological damage.

In people aging with HIV, nominating cognitive sentiments was associated with a pathway for greater prevalence of clinically important depression when these people also had work problems. In a cohort of working Canadians, work productivity was reduced in 79% of the people with an episode of depression over the last 12-months (71). In depressed people, moderate effect sizes were observed in neurocognitive domains of attention, executive function, learning, processing speed and memory (72, 73). Cognitive dysfunction was also a characteristic symptom in people with melancholic depression (74). Severity, frequency, and duration of depressive episodes as well as comorbidities were independently correlated with cognitive dysfunction (75-77).

Frequently reported correlates of anxiety in people with HIV include female sex, older age, lower education, bullying, sexual abuse, stigma, poor adherence to medication, and a lack of social support (78). Anxiety sentiments (i.e., fear, worry, stress, uncertainty, secrecy, shame, stigma) and other predictors are incorporated into the CaRT model. Another study estimated that the odds of anxiety increase threefold in people with HIV with perceived stigma(79). About three-fourths of those experiencing major depressive disorder were associated with anxious or distressed specifier (OR, 5.7; 95% CI: 4.98-6.5) (66).

A systematic review of the patient experiences with depression and anxiety in people with chronic conditions emphasized focus on a broad range of psychological responses(80). As shown in our previous study, more than two-thirds of the people meeting the threshold on a brain health concern also exceeded the threshold on at least one more outcome. Thus, the comorbidity of brain health concerns in people again with HIV is higher when compared to the estimates in the general population. Our approach provides insights as to how a patient-oriented approach using the PGI can be used to quickly assess the presence of brain health concerns.

A limitation of the model was the exclusion of some of the important other predictors (age, education, and satisfaction with sexuality), since these were modelled as non-binary while the CaRT models included only binary variables. The logistic regression in our previous study produced better estimates of goodness of fit and such results may be attributed to the inclusion of all other predictors. The CaRT model and the pathways are easier to grasp and provide additional information about people with greater prevalence of brain health concerns.

6.9-Conclusions

Category coding of high-risk sentiments provides a framework that can be applied for the assessment of brain health outcomes in people with HIV. The proposed framework identified the sentiments that are associated with a greater prevalence of brain health challenges including psychological distress, depression, anxiety, and cognitive difficulties. Emotional sentiments had a strong association with all outcomes considered. Cognitive sentiments were associated with both cognitive difficulties and clinically important depression. Work status was an important contributor for predicting all SROs. Positive sentiments were protective of depression for people not nominating cognitive sentiments but who had work problems. Also, positive sentiments were protective of low cognitive ability when people had work problems but did not nominate cognitive sentiments. The identification of the likelihood of presenting brain health concerns in people with HIV is complex, whereas decision tree models show that sentiment analysis of the PGI can identify the segments of people at a higher risk of developing brain health concerns.

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Tables and Figures

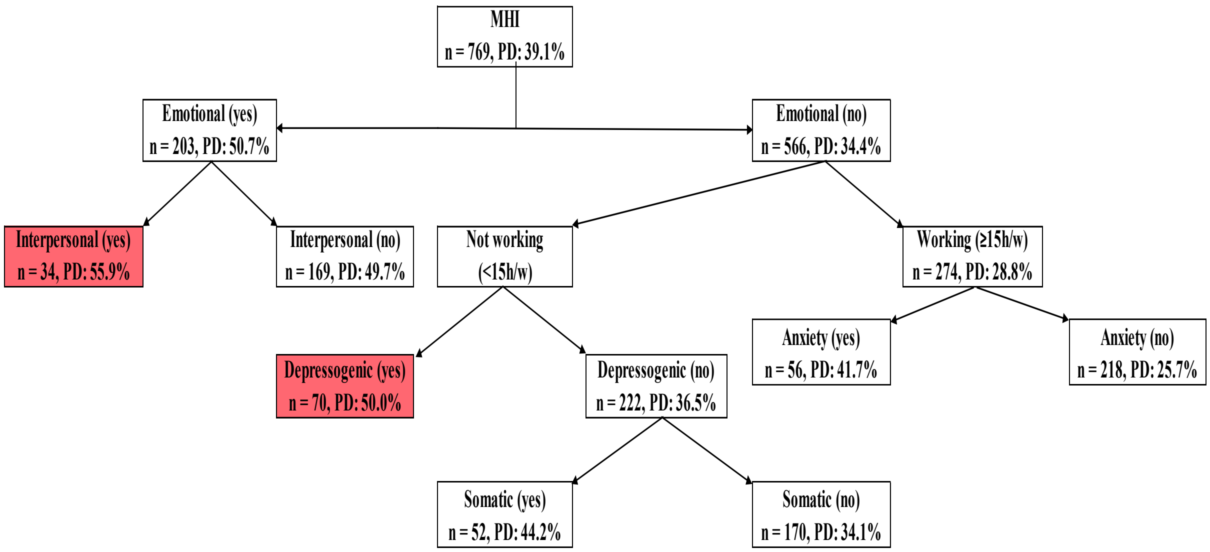
Table 1: Sentiments extracted from the life-areas nominated on the PGI

Sentiment categories	**Examples**
Emotional	Depressed mood, burden, end of life, death, emotional instability
Inter-personal	Detachment from people, isolation, need to have children, separation
Somatic	Insomnia, side-effects, pain, too much sleep, skin issues
Depressogenic	Self-esteem, loss of ego, less attractive, self-control, self-withdrawal
Anxiety	Fear, discretion, worry, fear of rejection, guilt, stigma, nervousness
Cognitive	Memory, sharpness, concentration, cognitive troubles, decision making
Positive	Hope, positive outlook on life, calm, less angry, positive sex life, new experiences

Table 2: Socio-demographic and clinical characteristics of the sample

Assessment	Study entry
	N (%) or mean ± SD
Sex, male	677 (84.9%)
Age, Mean ± SD	52.9 ± 8.2
Education	
No education or only kindergarten	35 (4.5%)
Primary school	209 (27.0%)
High school	268 (34.6%)
CEGEP/College	184 (23.8%)
University	78 (10.1%)
Satisfaction with sexuality	
Very dissatisfied	155 (20.1%)
Dissatisfied	161 (20.9%)
Neither satisfied nor dissatisfied	225 (29.2%)
Satisfied	176 (22.8%)
Very satisfied	55 (7.1%)
Working (paid work ≥15 h/w)	364 (45.9%)
Good physical function (score of ≥ 45/100)	726 (93.6%)
HIV Immune Markers	
Current CD4 in cells/mm3	636.3 ± 283.2
Nadir CD4 in cells/mm3	218.0 ± 171.4
HIV viral load (VL), undetectable (VL≤50 copies/mL)	710 (92.2%)
Years since HIV diagnosis	16.8 ± 7.9

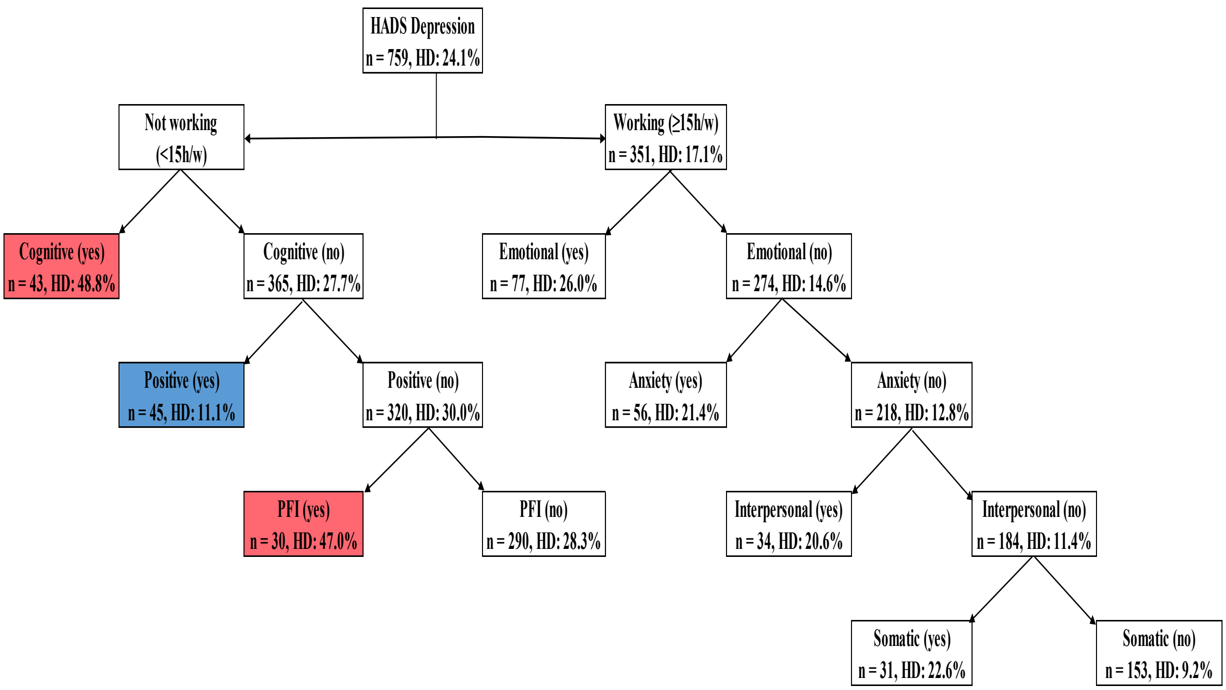
Figure 1: Regression tree for people meeting the threshold for psychological distress in the +BHN cohort



Red coloured terminal nodes represent the pathway to people having greater prevalence of psychological distress

*PD: Symptom probability indicative of psychological distress

Figure 2: Regression tree for people meeting the threshold for clinically important depression using the HADS-D in the +BHN cohort

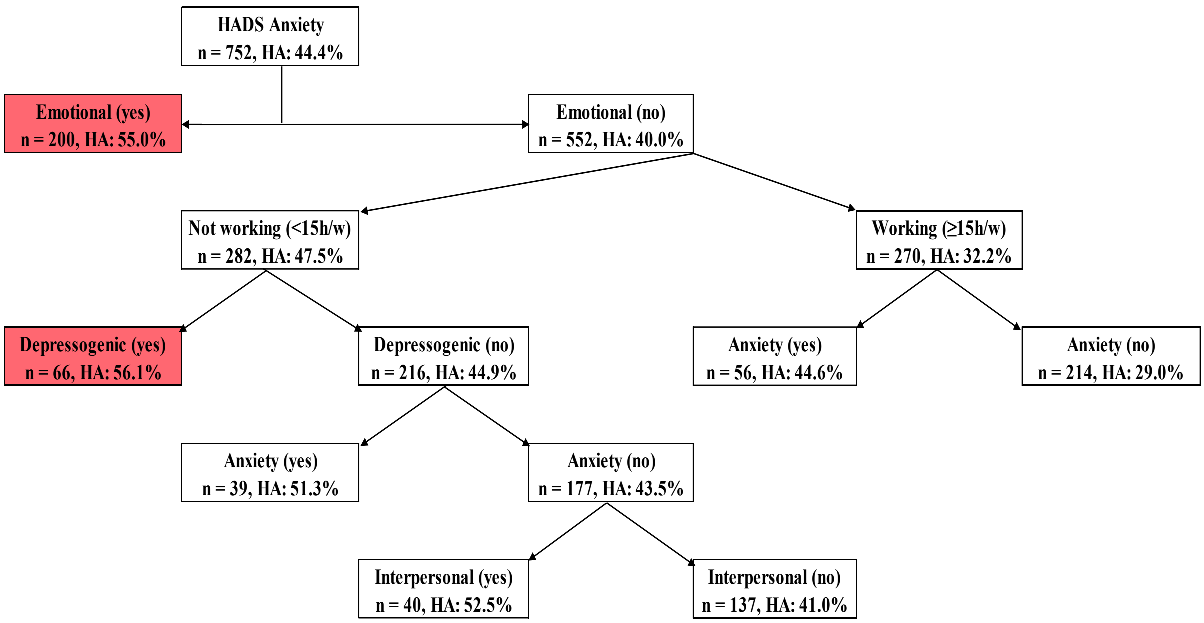


Red coloured terminal nodes represent the pathway to people having greater prevalence of clinically important depression

Blue coloured terminal node shows that positive sentiments are protective of depression

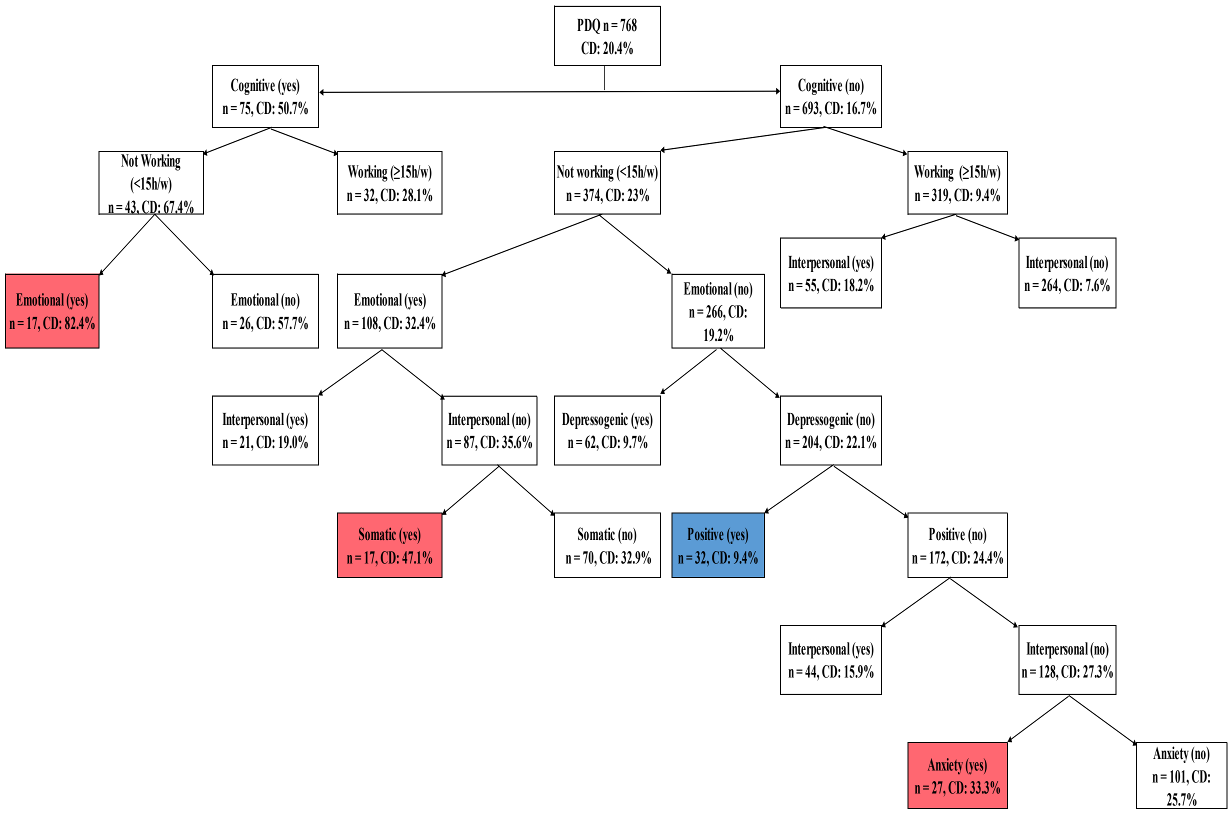
*HD: Symptom probability indicative of clinically important depression

Figure 3: Regression tree for people meeting the threshold for clinically important generalized anxiety in the +BHN cohort



Red coloured terminal nodes represent the pathway to people having greater prevalence of clinically important generalized anxiety
*HA: Symptom probability indicative of clinically important generalized anxiety

Figure 4: Regression tree for people meeting the threshold cognitive difficulties in the +BHN cohort



Red coloured terminal nodes represent the pathway to people having greater prevalence of cognitive difficulties
Blue coloured terminal node shows that the positive sentiments were protective of cognitive function
*CD: Symptom probability indicative of cognitive difficulties

Table 3: Pathways that lead to people having a greater prevalence of a specific brain health concern in the +BHN cohort

3-a) Pathways that lead to people having a greater prevalence of psychological distress							
Overall prevalence of psychological distress in the +BHN cohort using the MHI (n=769)							39.1*
Relative importance (%)	100.0	65.0	55.0	52.0	35.0	28.0	
Factors	Emotional	Not working	Depressogenic	Anxiety	Somatic	Interpersonal	
Pathway 1							50.0*
Pathway 2							55.9*

3-b) Pathways that lead to people having greater prevalence of clinically important depression											
Overall prevalence of clinically important depression in the +BHN cohort using the HADS-D (n=759)											24.1*
Relative importance (%)	100.0	75.0	67.0	56.0	55.0	44.0	37.0	29.0	11.0	11.0	
Factors	Not working	Cognitive	Positive	Emotional	PFI	Somatic	Anxiety	Interpersonal	Depressogenic	Sex	
Pathway 1											47.0*
Pathway 2											48.8*

3-c) Pathways that lead to people having a greater prevalence of clinically important generalized anxiety							
Overall prevalence of clinically important generalized anxiety in the +BHN cohort using the HADS-A (n=752)							44.4*
Relative importance (%)	100.0	99.0	62.0	50.0	39.0	35.0	
Factors	Not working	Emotional	Anxiety	Depressogenic	Somatic	Interpersonal	
Pathway 1							55*
Pathway 2							56.1*

3-d) Pathways that lead to people having greater prevalence of cognitive difficulties in the +BHN cohort										
Overall prevalence of cognitive difficulties using the PDQ (n=768)										20.4*
Relative importance (%)	100.0	88.0	51.0	42.0	42.0	30.0	21.0	13.0	10.0	
Factors	Cognitive	Work	Emotional	Interpersonal	Depressogenic	Positive	Somatic	Anxiety	Sex	
Pathway 1										33.3*
Pathway 2										47.1*
Pathway 3										82.4*

Red colored boxes represent the presence of the variable
Green colored boxes represent the absence of the variable

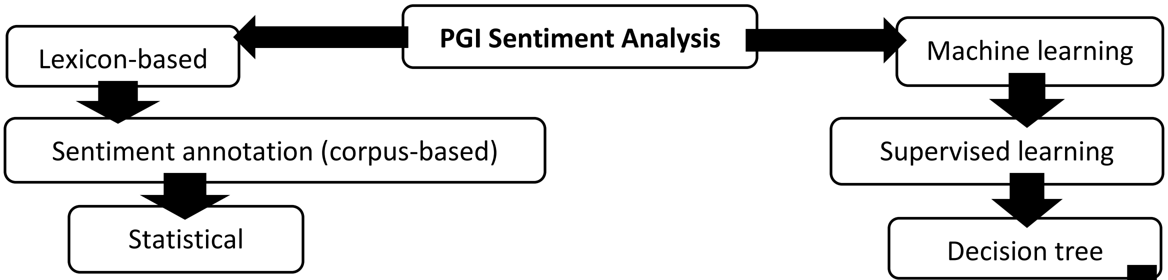
*Symptom probability indicative of a specific brain health concern (%)

CHAPTER 7: Integration of the manuscript 1 and manuscript 2

In the first manuscript, I identified the important sentiment categories that are predictive of the outcomes associated with psychological distress, depression, anxiety, and cognitive impairment. The self-nominated life areas from the Patient Generated Index (PGI) were categorized in terms of high-risk sentiment categories of emotional, interpersonal, somatic, depressogenic schemata, anxiety, and cognitive sentiments. A separate category was formed for positive sentiments. The results revealed good to excellent prediction of the measures associated with brain health concerns. Emotional and cognitive sentiments were predictive of all self-report outcomes. Positive sentiments were protective of depression and cognitive difficulties. The results showed that the PGI provides a quick and efficient means of predicting brain health concerns without the need to administer the Hospital Anxiety and Depression subscale for depression (HADS-D) and anxiety (HADS-A), Mental Health Index (MHI) and the Perceived Deficits Questionnaire (PDQ) or the Communicating Cognitive Concerns Questionnaire (C3Q).

The second manuscript takes a different approach to answer the same question. Here we use decision tree analysis modeling of sentiments to estimate the extent to which a self-nomination of areas related to mood, anxiety, and cognition on the PGI is associated with people having a greater prevalence of psychological distress, depression, anxiety, and cognitive difficulties. A classification and regression tree (CaRT) model was applied to identify the most relevant and independent sentiments that contributed to each brain health concern. For people who were not working, nominating both cognitive and emotional sentiments resulted in the highest prevalence of the threshold value at 82.4%. Through this approach, we obtain additional insights into the pathways associated with having a greater prevalence of brain health challenges and the relative importance of each sentiment category at study entry.

Figure 1: Summary of results for Manuscript 1 and Manuscript 2



Summary of results (Manuscript 1):

- Emotional sentiments were predictive of all self-report brain health outcomes with odds ratios (OR) ranging from 1.61 to 2.00 and c-statistics > 0.73 (good to excellent prediction)
- Cognitive sentiments were predictive of all self-report brain health outcomes with OR ranging from 1.50 to 4.78 and c-statistics > 0.72
- Nominating an anxiety sentiment was specific to predicting anxiety and psychological distress at any visit (OR: 1.65 & 1.52)
- Positive sentiments were predictive of good cognitive function (OR: 0.36) and protective of depressive symptoms (OR: 0.55)

Summary of results (Manuscript 2):

- The classification and regression tree (CaRT) model showed two pathways each for psychological distress, depression, anxiety, and three pathways for cognitive difficulties; a standardized difference of 10% was used to identify the pathways associated with a greater prevalence of the threshold value
- Cognitive sentiments were the most discriminatory for self-reported cognitive difficulties followed by work status, emotional, somatic and anxiety sentiments
- Emotional sentiments were the most discriminatory for both psychological distress and anxiety
- For people nominating cognitive sentiments, the prevalence of self-reported cognitive difficulties was 50.7% (20.1% overall prevalence for the BHN cohort), when not working (defined as <15 hours/week of paid employment) and also nominating emotional sentiments, the prevalence rate was 82.4%
- For those not working and nominating cognitive sentiments, the prevalence of clinically important depression was almost twice (48.8%) that of the overall prevalence for the cohort (24.1%), while those not working and not nominating cognitive sentiments, nominating positive sentiments was protective of cognitive function with a prevalence rate of 11.1%; those not nominating positive sentiments either but with poor physical function, the prevalence was 47.0%
- For people nominating emotional sentiments, the prevalence of clinically important anxiety was 55.0% (44.4% overall prevalence for the cohort), and for those not nominating emotional sentiments, not working and nominating depressogenic sentiments had a prevalence of 56.1%

CHAPTER 8: Discussion and conclusion

8.1-Discussion

In research people are often asked to fill out questionnaires about their health and functioning which often contain items that reflect serious health concerns such as those related to brain health. A worry is that responses to these questions may not be processed by anyone but a statistician. Some questionnaires lend themselves more readily for immediate processing by those conducting data collection. Individualized or personalized measures ask people to spontaneously nominate life-areas related to their condition that affects their quality of life (QOL). The responses in the persons own words are more readily interpreted and can indicate concerns that need further investigation. However, information on the extent to which the content spontaneously nominated by respondents to these measures reflect these concerns is under investigated. The overall aim of this thesis was to take important steps towards supporting this 'semi-qualitative' approach as an early-warning system to for brain health concerns. The measure under study in this thesis was the Patient Generated Index (PGI).

Although, the PGI has immense potential for use in clinical and research settings, it is important that the information gathered is interpreted with respect to more standardized methods of obtaining this information on related constructs. While the PGI, has been used in HIV, its use was confined to generating the most impactful areas and among the top 10 were emotional function, cognition, and fatigue. The relationship between the brain health areas nominated and results on standardized measures has not been investigated in people with Human Immunodeficiency Virus (HIV) and provides valuable information to support the clinical usefulness of the PGI.

One challenge with using the PGI is to interpret the text threads people use to express their health concerns. Concerning brain health states such as psychological distress, depression, anxiety, and lower cognitive function could be detected using sentiment analysis.

Sentiment analysis or opinion mining is the automatic processing of sentiments, opinions, and subjectivity within textual data (187). Emotion recognition and sentiment analysis are important areas in natural language processing (NLP) (188). Emotion detection is the means to identify distinct human emotion types, while sentiment analysis is associated with the detection of polarity (i.e., negative, positive, or neutral) (188). These terms are often used interchangeably for the identification of human emotion types and for the detection of polarity.

The first manuscript of this thesis used sentiment analysis of the self-nominated areas identified on the PGI. This longitudinal study applied sentiment analysis to the text-threads available from the PGI at study entry to predict brain health outcomes at this same first assessment and at subsequent assessments conducted at 9-month intervals over a period of 27-months. The results, summarized below in Figure 1, support the value of the PGI in predicting brain health outcomes of psychological distress, depression, anxiety, and low cognitive ability assessed using standardized measures of these constructs. Emotional and cognitive sentiments were predictive of all outcomes used in our analyses.

Figure 1: Summary of results for Manuscript 1

Summary of Results for important sentiments adjusted for other predictors

Adjusted: Sentiments + Other predictors	C-statistics at study entry (goodness of fit of logistic models)				Linear models
	HADS-D (183/768)	HADS-A (334/759)	MHI (301/778)	PDQ/C3Q (157/779)	B-CAM (n=731)
	c-statistic				b (se) [t]
Emotional	0.749	0.740	0.733	0.736	
Somatic					-3.04 (1.29) [-2.36]
Anxiety		0.740			
Cognitive	0.741	0.735	0.729	0.745	
Positive	0.741			0.737	
	First assessment at study entry to any assessment adjusted sentiment analysis				
	HADS-D (628/2669) OR (95% CI)	HADS-A (1121/2661) OR (95% CI)	MHI (1004/2692) OR (95% CI)	PDQ/C3Q (328/1957) OR (95% CI)	B-CAM (n=2635) b (s.e) [z]
Emotional	1.83 (1.37-2.45)	1.77 (1.34-2.35)	1.61 (1.22-2.13)	2.00 (1.41-2.82)	
Somatic					-2.21 (1.18) [-1.87]
Anxiety		1.65 (1.20-2.26)	1.52 (1.12-2.06)		
Cognitive	1.69 (1.10-2.61)	1.39 (0.92-2.11)	1.61 (1.08-2.40)	4.78 (3.10-7.39)	
Positive	0.55 (0.33-0.91)			0.36 (0.19-0.67)	

- All models were adjusted for important sentiments, centre, and all other predictors (age, sex, education, work status, satisfaction with sexuality and physical function
- Emotional sentiments were predictive of all self-report brain health outcomes
- Cognitive sentiments were predictive of all self-report brain health outcomes with OR ranging from 1.50 to 4.78 and c-statistics > 0.72
- Nominating an anxiety sentiment was specific to predicting anxiety and psychological distress at any visit (OR: 1.65 & 1.52)
- Positive sentiments were predictive of good cognitive function (OR: 0.36) and protective of depressive symptoms (OR: 0.55)
- Somatic sentiments were predictive of performance-based B-CAM

The second manuscript takes a different approach to the same question, a decision tree approach. Instead of identifying what sentiments relate to brain health outcomes, as in the first paper, the question relates more to how people with these concerning brain health outcomes express sentiments. By taking this approach is possible to identify the kinds of sentiments that people with these health outcomes use to express their feelings. In this paper, I have called these different sentiments, pathways to an outcome. The decision tree analysis also provides estimates of the relative importance of sentiments that distinguish between people with and without these concerning brain health outcomes. Table 1 presents the pathways that lead to the highest prevalence of each brain health concern for the Positive Brain Health Now (+BHN) cohort.

Table 1: Summary of Results for Manuscript 2

Branches leading to the highest cumulative proportion of people meeting the threshold for a brain health concern		**% Meeting the threshold**
Psychological distress ≥ 60/100 on Mental Health Index (MHI) of the RAND-36	Overall	39.10%
Nominated depressogenic sentiments, not working (<15h/w) and did not nominate emotional sentiments		50.00%
Nominated emotional sentiments		50.70%
Nominated both emotional and interpersonal sentiments		55.90%
Clinical depression ≥ 8/21 on the Hospital Anxiety and Depression subscale for depression (HADS-D)	Overall	24.10%
Not working and with poor physical function (<45/100 on the Physical Function Index of the RAND-36)		47.00%
Nominated cognitive sentiments and not working		48.80%
Generalized anxiety ≥ 8/21 on the Hospital Anxiety and Depression subscale for anxiety (HADS-A)	Overall	44.40%
Nominated emotional sentiments		55.00%
Nominated depressogenic sentiments, not working and did not nominate emotional sentiments		56.10%
Lower cognitive ability (<50/100 on the Communicating Cognitive Concerns Questionaire-C3Q)	Overall	20.40%
Nominated emotional sentiments and not working, and did not nominate cognitive sentiments		32.40%
Nominated anxiety sentiments and not working (did not nominate cognitive, emotional, depressogenic, positive, and interpersonal sentiments		33.30%
Nominated emotional sentiments, not working, and additionally nominated somatic sentiments (did not nominate cognitive sentiments)		47.10%
Nominated cognitive sentiments		50.70%
Nominated cognitive sentiments, not working, and additionally nominated emotional sentiments		82.40%

The presence of emotional sentiments was indicated for greater prevalence of symptoms associated with psychological distress, depression, and anxiety. Cognitive sentiments were associated with a greater prevalence of both lower cognitive ability and depression. Work status was an important other contributor for all SROs. Physical function was associated with a greater prevalence of depression. Also, positive sentiments were protective of depressive symptoms and cognitive function.

8.2-Lessons learned

This project provided me with many opportunities to explore new and unfamiliar concepts. Initially, I was introduced to a mix of research in fields including epidemiology both clinical and environmental, brain health, outcome evaluation and research, patient-centered outcomes, sentiment analysis, and NLP. Learning more about health outcomes research has enabled me to observe the world from a different lens.

My perspectives continue to evolve every day owing to this exposure. I developed an assortment of skills, working on the manuscripts, analytical software, coursework and towards the goals of my overall thesis. I have developed the skills to write more concisely, effectively, and efficiently. I have also learned to use the SAS version 9.4 (previously "Statistical Analysis System") for conducting the analyses required for my project. Working on my thesis has enabled me to be more analytical and adopt a more systematic approach to everything I do. On a different note, I learned the many steps involved in conducting research including an in-depth review of the literature. I learned that research requires an incredible amount of patience, reflection, and hard work. Lastly, I learned not to be scared of trying new things and to continue my efforts for personal development going forward.

8.3-Next steps

It is argued that the best results for sentiment analysis are realized with trained human or crowd coding while machine learning noticeably out-performs dictionary-based methods (222). Although, human coding of sentiments is optimal, such methods can be tedious and difficult to replicate (248). So, computational approaches can allow scalability and replicability for sentiment analysis (222). Successful deployment of artificial intelligence (AI) in healthcare requires a robust clinical evaluation (249).

The next steps for the PGI sentiment analysis project consist of a collaboration with Dr. Marie-Jean Meurs (also a member of my thesis committee) and her team at the Department of Computer Science at the University of Quebec in Montreal (UQAM). The objective is to estimate the extent to which NLP can predict the prevalence of sentiments using a robust classification of sentiments emerging from the areas nominated on the PGI.

Supervised machine learning experiments will be conducted to identify the models that best replicate the sentiments from human curated data for the PGI, used as the "gold standard" (250). The textual data from the PGI will be used to train algorithms for search, extraction, classification and for measuring the accuracy of such algorithms (251). Supervised learning can expedite these analyses to quickly assess new data (252). It is imperative that automatic text analysis methods are then validated to ensure the efficiency of such analyses (253). The machine learning models that can be used for such experiments include the support vector machine (SVM), random forest (RF), logistic regression, multi-layer perception (MLP), and transformers such as the Bidirectional Encoder Representations from Transformers (BERT) and/or the XLNet (an extension of the Transformer-XL model pre-trained using an autoregressive method) using 5-fold cross-validation.

More recently, a systematic review of the sentiment analysis literature in health and well-being found that the SVM was the most popular model; however, decision trees often outperformed (193). The Pareto principle (the 80-20 rule or law of a vital few) states that for many events approximately 80% of the outcomes (or outputs) result from 20% of all causes (254) and is a useful concept to apply in the context of machine learning (255). The supervised machine learning models are often trained on 80% of data while performance is evaluated on the other 20%.

The results for all selected models can be consistently assessed using the F1-score which measures a model's accuracy on a dataset (256). This score is used to evaluate the binary classification systems which classify the PGI text threads. The F1-score is defined as the harmonic mean of two other metrics known as precision and recall, with the highest possible value of 1.0 indicating perfect precision, or that a model perfectly classifies each observation into the correct class, and the lowest possible value of 0 if either precision or recall is zero (257). Precision is the positive predictive value or the fraction of relevant instances among retrieved instances while recall (also called sensitivity) is the fraction of relevant instances that were retrieved (258). In pattern recognition, information retrieval, and classification, precision and recall are performance metrics relevant to data from a collection, corpus, or a sample space (259).

8.4-Conclusion

My thesis and the next steps are aimed at providing the evidence needed to validate and promote the use of the PGI for detecting brain health concerns early-on in the clinical and research settings. The objective is to ensure the effective use of this knowledge gathered from sentiment analysis to improve the existing procedures used to detect brain health concerns. Instead, the self-nomination of 5 life-areas on the PGI may replace several questionnaires used to assess psychological distress, depression, anxiety, and lower cognitive function after cross-validation of this approach across populations with different chronic concerns.

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APPENDICES

Appendix 1: Patient Generated Index scoring sheet (French version)

Demander au participant de vous décrire comment le VIH affecte sa vie et ses activités.
Veuillez inscrire les réponses dans le tableau suivant.

**** Instructions pour l'interviewer**** *Regarder la page 3 pour savoir comment remplir la feuille.*

Étape 1: Aspects affectés par la SEP	**Étape 2: Valeur attribuée**	**Étape 3: Points attribués**
Tous les autres aspects de votre vie que vous n'avez pas mentionnés		

Étape 1

Questions au participant:
Pensez aux aspects de votre vie qui sont les plus affectés par le VIH.
Donnez nous au moins 5 réponses.

Instruction pour l'interviewer:
Inscrivez les réponses dans les cases.

Étape 2

Questions au participant:
Donnez une valeur aux aspects que vous avez identifiés dans l'étape 1.
Référez vous au <u>*dernier mois*</u> pour établir la valeur.

Instruction pour l'interviewer:
Montrez l'échelle de 1 à 10 au participant et écrivez les réponses dans les cases.

Étape 3

Questions au participant:
Imaginez quels aspects de votre vie vous souhaiteriez voir s'améliorer. Nous vous donnons 12 points imaginaires que vous devez placer dans les cases en fonction de votre désir de voir cet aspect amélioré. Plus vous voulez que cet aspect soit amélioré, plus vous mettez de points et moins cet aspect vous importe, moins vous en mettez! Vous devez inclure dans votre calcul la dernière option (6) « Tous les autres aspects de votre vie que vous n'avez pas mentionnés». Vous n'êtes pas obligé de mettre des points dans chaque case mais cela doit donner 12 points au total. Vous ne pouvez donner moins ou plus de 12 points au total!

Instruction pour l'interviewer:
Écrivez les réponses dans la case 3 et assurez-vous de ne pas dépasser la limite de 12 points.

Exemple:

- Un participant a identifié 2 aspects très affectés par son VIH
- 1. La marche est extrêmement affectée et il aimerait voir cet aspect s'améliorer de beaucoup.
- 2. Son sommeil est affecté et il aimerait que cet aspect s'améliore un peu.
- 3. Les autres aspects ne sont pas si mal mais il aimerait que certains s'améliorent.

Étape 1: **Aspects affectés par la SEP**	**Étape 2:** **Valeur attribuée**	**Étape 3:** **Points attribués**
Marcher	0	6
Dormir	5	1
Tous les autres aspects de votre vie que vous n'avez pas	7	5

10 =Exactement comme vous voudriez que ce soit
9 = Près de comment vous voudriez que ce soit
8 = Très bien, mais pas exactement comme vous voudriez que ce soit
7 = Bien, mais pas comme vous voudriez que ce soit
6 = Entre bien et moyen
5 = Moyen
4 = Entre mauvais et moyen
3 = Mauvais, mais pas le pire que vous pouvez imaginer
2 = Très mauvais, mais pas le pire que vous pouvez imaginer
1 = Proche du pire que vous pouvez imaginer
0 = Le pire que vous pouvez imaginer

Appendix 2 : Questionnaires at study entry

Questionnaires
Baseline

Principal Investigators:

Understanding and Optimizing Brain Health in HIV Now

Dr. Lesley Fellows and Dr. Marie-Josée Brouillette

This study aims to identify, understand and optimize brain health in people living with HIV. A longitudinal cohort of aging HIV positive individuals will be followed over 27 months using a multiple randomized control trial platform. The information collected, will contribute to new knowledge on neurocognitive decline providing insights into the natural history and impact of cognitive symptoms and deficits, allowing us to define the heterogeneity underlying poor brain health, and for those who report good brain health at baseline, shedding light on the incidence of cognitive deficits in this aging population.

Patient ID　　　　DD　　　　MMM　　　　YYYY

☐☐☐☐☐　　　　☐☐ / ☐☐☐ / ☐☐☐☐

If you have any questions or concerns, please contact us at: pozbhn.med@mcgill.ca

EQ-5D

Please indicate which statement best describes your own health state today. Do not tick more than one box in each group.

Mobility

I have no problems in walking about ❒

I have some problems in walking about ❒

I am confined to bed ❒

Self-Care

I have no problems with self-care ❒

I have some problems washing or dressing myself ❒

I am unable to wash or dress myself ❒

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ❒

I have some problems with performing my usual activities ❒

I am unable to perform my usual activities ❒

Pain / Discomfort

I have no pain or discomfort ❒

I have moderate pain or discomfort ❒

I have extreme pain or discomfort ❒

Anxiety / Depression

I am not anxious or depressed ❒

I am moderately anxious or depressed ❒

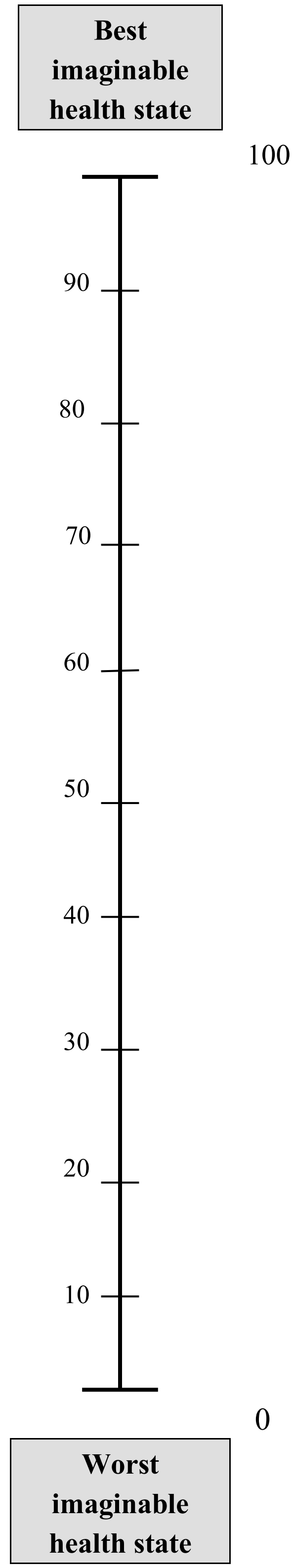
I am extremely anxious or depressed ❒

Patient ID: ________________

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad is your own health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.

Your own health state today



Patient ID: ________________

MOS-36: GENERAL HEALTH PERCEPTION SUBSCALE

1. In general, would you say your health is:

- ☐ Excellent
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor

2. Compared to 1 year ago, how would you rate your health in general now?

- ☐ Much better now than one year ago
- ☐ Somewhat better now than one year ago
- ☐ About the same
- ☐ Somewhat worse now than one year ago
- ☐ Much worse now than one year ago

3. How TRUE or FALSE is <u>each</u> of the following statements for you.

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
3. I seem to get sick a little easier than other people					
4. I am as healthy as anybody I know					
5. I expect my health to get worse					
6. My health is excellent					

Patient ID: ________________

RASCH: MOTIVATION/APATHY

Item	Not at all	Slightly	Some	A lot
1. Are you always looking for something to do?				
2. Do you have energy for daily activities?				
3. Are you interested in learning new things?				
4. Does anything interest you?				
5. Do you have motivation?				
6. Do you put much effort into things?				

Patient ID: ________________

OARS: SOCIAL SUPPORT

1. How many people do you know well enough to visit within their homes?

- ☐ five or more
- ☐ Three to four
- ☐ one to two
- ☐ none

2. About how many times did you talk to someone (friends, relatives or others) on the telephone in the past week? (either you called them or they called you, or sent text messages) If the subject has no phone, the question still applies.

- ☐ once a day or more
- ☐ 2 – 6 times
- ☐ once
- ☐ not at all

3. How many times during the past week did you spend some time with someone who does not live with you, that is you went to see them or they came to visit you or you went out to do things together?

- ☐ once a day or more
- ☐ 2 – 6 times
- ☐ once
- ☐ not at all

4. Do you have someone you trust and can confide in?

- ☐ yes
- ☐ no

5. Do you find yourself feeling lonely quite often, sometimes or almost never?

- ☐ quite often
- ☐ sometimes
- ☐ almost never

6. Do you see your relatives and friends as often as you want to or are you somewhat unhappy about how little you see them?

☐ as often as wants to

☐ somewhat unhappy about how little

7. Is there someone who would give you any help at all if you were sick or disabled, for example, your husband / wife, a member of your family or a friend?

☐ yes

☐ no one willing and able

If yes, ask a) and b)

a) Is there someone who would take care of you as long as you needed, or only for a short time, or only someone who would help you now and then (for example, taking you to the doctor or fixing lunch occasionally, etc.)

☐ someone who would take care of the subject indefinitely (as long as needed)

☐ someone who would take care of the subject for a short time (a few weeks to six months)

☐ Someone who would help the subject now and then (taking him to the doctor, fixing lunch, etc.)

b) Who is this person? Relationship: ___________________________

Patient ID: ________________

STANFORD SELF EFFICACY

We would like to know how confident you are in doing certain activities. For each of the following questions, please choose the number that corresponds to your confidence that you can do the tasks regularly at the present time.

	1 Not at all confident	2	3	4	5	6	7	8	9	10 Totally confident
1. How confident are you that you can keep the fatigue caused by your medical condition from interfering with the things you want to do?										
2. How confident are you that you can keep the physical discomfort or pain of your medical condition from interfering from the things you want to do?										
3. How confident are you that you can keep the emotional distress caused by your medical condition from interfering from the things you want to do?										
4. How confident are you that you can keep any other symptoms or health problems you have from interfering from the things you want to do?										
5. How confident are you that you can do the different tasks and activities needed to manage your health condition so as to reduce your need to see a doctor?										
6. How confident are you that you can do things other than just taking medication to reduce how much your medical condition affects your everyday life?										

LIFE ENGAGEMENT TEST

Please answer the following questions about yourself indicating the extent to which you agree or disagree with each statement

	Strongly disagree	Disagree	Neither agree or disagree	Agree	Strongly agree.
1. There is not enough purpose in my life					
2. To me, the things I do are all worthwhile					
3. Most of what I do seems trivial and unimportant to me					
4. I value my activities a lot					
5. I don't care very much about the things I do					
6. I have lots of reasons for living					

Patient ID: ________________

SIGNS & SYMPTOMS

Below is a list of potential symptoms that you may be experiencing today. If you have the symptom, rate the degree of INTENSITY that best decribes the extent of the symptom. If you do not have the symptom, check the "absent" box.

Intensity				Symptoms
Absent	**Mild**	**Moderate**	**Severe**	
☐	☐	☐	☐	Weakness
☐	☐	☐	☐	Loose Stools
☐	☐	☐	☐	Diarrhea
☐	☐	☐	☐	Dizziness
☐	☐	☐	☐	Headaches
☐	☐	☐	☐	Weight gain in stomach area
☐	☐	☐	☐	Hump on back of neck/shoulders
☐	☐	☐	☐	Skinny arms and legs
☐	☐	☐	☐	Prominent leg veins
☐	☐	☐	☐	Numbness/tingling of feet/toes

Patient ID: ________________

HOSPITAL ANXIETY & DEPRESSION SCALE

Read each item and place a firm tick in the box opposite the reply, which comes closest to how you have been feeling in the past week. Don't take too long over your replies: Your immediate reaction to each item will probably be more accurate than a long thought out response. Tick only one box in each section

Q1. I feel tense or wound up: ☐ Most of the time ☐ A lot of the time ☐ Time to time ☐ Not at all	**Q8. I feel as if I am slowed down:** ☐ Nearly all the time ☐ Very often ☐ Sometimes ☐ Not at all
Q2. I get a sort of frightened feeling like butterflies in the stomach: ☐ Most of the time ☐ A lot of the time ☐ Time to time ☐ Not at all	**Q9. I still enjoy the things I used to enjoy:** ☐ Definitely as much ☐ Not quite so much ☐ Only a little ☐ Hardly at all
Q3. I get sort of frightened as if something awful is about to happen: ☐ Very definitely and quite badly ☐ Yes, but not too badly ☐ A little, but it doesn't worry me ☐ Not at all	**Q10. I have lost interest in my appearance:** ☐ Definitely ☐ I don't take so much care as I should ☐ I may not take quite as much care ☐ I take just as much care as ever
Q4. I can laugh and see the funny side of things: ☐ As much as I always could ☐ Not quite as much now ☐ Definitely not so much now ☐ Not at all	**Q11. I feel restless as if I have to be on the move:** ☐ Very much indeed ☐ Quite a lot ☐ Not very much ☐ Not at all
Q5. Worrying thoughts go through my mind: ☐ A great deal of the time ☐ A lot of the time ☐ From time to time but not too often ☐ Only occasionally	**Q12. I look forward with enjoyment to things:** ☐ As much as ever I did ☐ Rather less than I used to ☐ Definitely less than I used to ☐ Hardly at all
Q6. I feel cheerful: ☐ Not at all ☐ Not often ☐ Sometimes ☐ Most of the time	**Q13. I get sudden feelings of panic:** ☐ Very often indeed ☐ Quite often ☐ Not very often ☐ Not at all
Q7. I can sit at ease and feel relaxed: ☐ Definitely ☐ Usually ☐ Not often ☐ Not at all	**Q14. I can enjoy a good book or radio or TV program:** ☐ Often ☐ Sometimes ☐ Not often ☐ Very seldom

PHYSICAL ACTIVITY

Patient ID: ________________

Which of the activities do you do regularly? If yes, how many hours in a typical week?

	No	**YES**	**If Yes, # of hours/wk**
1. Reading			
2. Watch TV			
3. Checking e-mail			
4. Surfing the internet			
5. Work on computer			
6. Games on computer			
7. Crafts/hobbies			
8. Light housework (ex. dusting, washing dishes)			
9. Heavy housework (ex. vacuuming)			
10. Light activities (ex. going for walk)			
11. Moderate activities (ex. dancing, golfing)			
12. Heavy vigorous activities that make you perspire (ex. jogging, swimming)			
13. Other: ______________________________			

Patient ID: ________________

NUTRITION

1. How many times a week do you eat food (meals or snacks) that has been prepared at a restaurant (eat in or take out), or by a caterer (i.e. not home-cooked)?

- ☐ Never or very rarely
- ☐ 1-2 times per week
- ☐ 3-5 times per week
- ☐ Daily or almost daily
- ☐ More than once per day

2. How many times per week do you eat a home-cooked dinner?

- ☐ Never or very rarely
- ☐ 1-2 times per week
- ☐ 3-4 times per week
- ☐ Every day or almost every day

Patient ID: ________________

WHOQOL HIV BREF

This assessment asks how you feel about your quality of life, health, or other areas of your life. **Please answer all the questions.** If you are unsure about which response to give to a question, **please choose the one** that appears most appropriate. This can often be your first response.
Please keep in mind your standards, hopes, pleasures and concerns.
We ask that you think about your life **in the last two weeks.**
Please read each question, assess your feelings, and choose the response on the scale for each question that gives the best answer for you.

	Very poor	Poor	Neither poor nor good	Good	Very good
1. How would you rate your quality of life?					

	Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2. How satisfied are you with your health?					

The following questions ask about how much you have experienced certain things in the last two weeks.

	Not at all	A little	A moderate amount	Very much	An extreme amount
3. To what extent do you feel that physical pain prevents you from doing what you need to do?					
4. How much are you bothered by any physical problems related to your HIV infection?					
5. How much do you need any medical treatment to function in your daily life?					
6. How much do you enjoy life?					
7. To what extent do you feel your life to be meaningful?					
8. To what extent are you bothered by people blaming you for your HIV status?					
9. How much do you fear the future?					

10. How much do you worry about death?					

	Not at all	A little	A moderate amount	Very much	Extremely
11. How well are you able to concentrate?					
12. How safe do you feel in your daily life?					
13. How healthy is your physical environment?					

The following questions ask about how completely you experience or were able to do certain things in the last two weeks.

	Not at all	A little	Moderately	Mostly	Completely
14. Do you have enough energy for everyday life?					
15. Are you able to accept your bodily appearance?					
16. Have you enough money to meet your needs?					
17. To what extent do you feel accepted by the people you know?					
18. How available to you is the information that you need in your day-to-day life?					
19. To what extent do you have the opportunity for leisure activities?					

	Very poor	Poor	Neither poor nor good	Good	Very good
20. How well are you able to get around?					

Patient ID: ________________

The following questions ask you how good or satisfied you have felt about various aspects of your life over the last two weeks.

	Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
21. How satisfied are you with your sleep?					
22. How satisfied are you with your ability to perform your daily living activities?					
23. How satisfied are you with your capacity for work?					
24. How satisfied are you with yourself?					
25. How satisfied are you with your personal relationship?					
26. How satisfied are you with your sex life?					
27. How satisfied are you with the support you get from your friends?					
28. How satisfied are you with the conditions of your living place?					
29. How satisfied are you with your access to health services?					
30. How satisfied are you with your transport?					

The following question refers to how often you have felt or experienced certain things in the last two weeks.

	Never	Seldom	Quite often	Very often	Always
31. How often do you have negative feelings such as blue mood, despair, anxiety, depression?					

Patient ID: ________________

WHO-5: WELL BEING INDEX

Please indicate for each of the five statements which is closest to how you have been feeling over the last two weeks.

Over the last 2 weeks	All of the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1. I have felt cheerful and in good spirits						
2. I have felt calm and relaxed						
3. I have felt active and vigorous						
4. I woke feeling fresh and rested						
5. My daily life has been filled with things that interest me						

Patient ID: ________________

MOS-35: MENTAL HEALTH

1. During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
1. Cut down the **amount of time** you spent on work or other activities		
2. **Accomplished less** than you would like		
3. Didn't do work or other activities as **carefully** as usual		

2. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
   - ☐ Not at all
   - ☐ Slightly
   - ☐ Moderately
   - ☐ Quite a bit
   - ☐ Extremely

Patient ID: _______________

MOS-36: VITALITY

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**.

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
Did you feel full of pep?						
Have you been a very nervous person?						
Have you felt so down in the dumps that nothing could cheer you up?						
Have you felt calm and peaceful?						
Did you have a lot of energy?						
Have you felt downhearted and blue?						
Did you feel worn out?						
Have you been a happy person?						
Did you feel tired?						

Patient ID: ________________

STANFORD PRESENTEEISM SCALE

The following sets of questions are work related questions. However, if you do not currently work, but are volunteering, you can answer the following questions based on your volunteer.

Will you be answering based on work or volunteer? __________

In thinking about how your HIV has affected your ability to do your job, how often in the past 4 weeks:

	Always	Frequently	About half the time	Occasionally	Never	No answer
1.Were you able to finish hard tasks?						
2.Did you find your attention wandering?						
3.Were you able to focus on achieving work goals?						
4.Did you feel energetic enough to work?						
5.Were the stresses of your job hard to handle?						
6.Did you feel hopeless about finishing your work?						
7.Were you able to focus on finding a solution when unexpected problems arose in your work?						
8.Did you need to take breaks from your work?						
9.Were you able to work with other people on shared tasks?						
10.Were you tired because you lost sleep?						

11. Given your HIV, what percentage of your usual productivity level were you able to achieve while working over the last 4 weeks? (Place X on continuous scale 0-100)

0	10	20	30	40	50	60	70	80	90	100

12. Because of your HIV, how many work hours did you miss in the past 4 weeks?
(0-40+ HOURS)

NUMBER OF HOURS ______________________

13. During the past 4 weeks, have you had any of the following problems with your work productivity as a result of your HIV?

	YES	NO
Cut down the amount of time you spent on work		
Accomplished less than you would like		
Were limited in the kind of work		
Had difficulty performing the work (it took extra effort)		

14. Think of a mentally challenging task at work, how can you do it now compared to one year ago?

☐ Much better now than a year ago
☐ Somewhat better now than a year ago
☐ About the same as one year ago
☐ Somewhat worse now than one year ago
☐ Much worse now than a year ago

Patient ID: ________________

SLEEP QUESTIONNAIRE

In the past month, how much of the time did you have difficulties **SLEEPING**?

Sleeping problem	SLEEPING PROBLEMS in past month		
Do you feel rested when you wake up?	*Always*	*Often*	*Never*
How long does it take you to fall asleep at night?	*< 10 minutes*	*10 to 30 min*	*40 to 90 min*
Do you wake up in the middle of the night?	*Not usually*	*1 to 2 times a week*	*3 or more times a week*
Do you take a nap during the day?	*Never*	*Sometimes*	*All the time*

Do you have vivid dreams and/or nightmares during your sleep? Yes ☐ No ☐

If yes, how many times a week? ____________

Patient ID: ________________

TICS

For the following questions, situations and experiences are described. Please respond with how many times each event has occurred during the last 3 months by checking the correct answer. Please answer all the questions in order without skipping any. Certain questions might appear similar to others, but please answer all of them. You don't have to rush. Take your time and think about each answer.

		During the last 3 months, I have found that...				
		Never	**Rarely**	**Sometimes**	**Often**	**Very often**
01	I worry that something unpleasant will happen					
02	I try, in vain, to gain recognition for my good work					
03	There are times when I have too many tasks to complete					
04	There are times when I cannot stop thinking about things that worry me					
05	Although I do my best my work is not appreciated					
06	I find that I have too much to do					
07	There are times when I worry a lot and cannot stop myself					
08	There are times when I can do what is expected of me					
09	There are times when my responsibilities to others are a burden					
10	There are times when I'm overwhelmed by work					
11	I worry about not being able to fulfill my duties					
12	There are times when anxiety overwhelms me					

PHYSICAL ACTIVITY QUESTION

Patient ID: ________________

1. What best describes your physical activity level in the past 6 months?
   - ☐ Vigorously active for at least 30 min, 3 times per week
   - ☐ Moderately active at least 3 times per week
   - ☐ Seldom active, preferring sedentary activities

Patient ID: ________________

Toxicology

Have you ever used or currently use any of the following drugs?

Drug	**Never Used**	**Currently Using (within past 3 months)**		**Previously Used (>3 months)**	
		Amount*	**Years**	**Amount***	**Years**
1. Heroin					
2. Cocaine					
3. Crack					
4. Crystal Meth					
5. THC/Marijuana					
6. Benzodiazepines					
7. Opiates/Opioids					
8. Methadone					
9. Other:_____________					

***Amount:**
1 = Occasionally (< 3 per month)
2 = Once or twice a week
3 = Daily - about once a day
4 = More than once daily
5 = Marijuana > 8 per day, 1 - 2 times per week

Have you ever attended a rehabilitation program (drugs, alcohol)? ☐ Yes ☐ No

INDIVIDUAL CHARACTERISTICS

1. What is the highest level of education that you have completed?

   - ☐ Primary School
   - ☐ High School
   - ☐ CEGEP/College
   - ☐ University
   - ☐ No education or only kindergarten

2. As a child:
   a. Have you ever failed a grade or course? ☐ Yes ☐ No
   b. Have you had any special help with classes when you were in school?
      ☐ Yes ☐ No
   c. Were you ever diagnosed as having a learning disability or attention deficit disorder? ☐ Yes ☐ No

3. Who do you currently live with?
   - ☐ Alone
   - ☐ Spouse or partner
   - ☐ Family Member
   - ☐ Friends
   - ☐ Other:_________________________

4. Are you single, married, widowed, divorced or separated?
   - ☐ Single
   - ☐ Married
   - ☐ Widowed
   - ☐ Divorced
   - ☐ Separated

INDIVIDUAL CHARACTERISTICS

5. Please check off which of the following ethnic groups your biological (blood) parents belong to:

	Father:			Mother:
☐	Aboriginal		☐	Aboriginal
☐	South Asia (East Indian, Pakistani, SriLanka)		☐	South Asia (East Indian, Pakistani, Sri Lanka)
☐	West Asia		☐	West Asia
☐	East Asia (Chinese, Vietnamese, Filipino, Korean)		☐	East Asia (Chinese, Vietnamese, Filipino, Korean)
☐	Arab		☐	Arab
☐	Asian		☐	Asian
☐	Black (Afro-Caribbean)		☐	Black (Afro-Caribbean)
☐	Latin American		☐	Latin American
☐	White (Caucasian)		☐	White (Caucasian)
☐	Other:___________________________		☐	Other:___________________________

6. During the past 6 months, how many days did you spend in bed ("lost days") due to an illness? ___________

7. History of traumatic brain injury:
   a. Have you ever had a blow to the head that resulted in a loss of consciousness of 30 minutes or more? ☐ Yes ☐ No
   b. Have you ever had a concussion (been knocked out or dazed after being hit on the head? Yes ☐ No ☐

      If yes, how many times (lifetime)? ___________

Patient ID: ________________

INDIVIDUAL CHARACTERISTICS

SMOKING TOBACCO:

1. Are you a current smoker?	
☐ Yes	☐ No
If yes, answer questions below	*If no, skip to question 2.*
a. Do you currently smoke tobacco: ☐ Regularly ☐ Irregularly (skip to question 2)	
*If you answered that you smoke **regularly** then answer questions below.*	
b. How old were you when you first started smoking tobacco regularly? __________	
c. On average how many cigarettes do you smoke per day? NUMBER OF CIGARETTES/DAY:________________	
d. On average, *over the entire time* you have smoked, how many cigarettes did you smoke per day? NUMBER OF CIGARETTES/DAY:_____________	

2. Are you a past smoker?	
☐ Yes	☐ No
If yes, answer questions below	*If no, skip to question 3.*
a. Did you smoke tobacco: ☐ Regularly in the past ☐ Irregularly in the past (skip to question 3)	
*If you answered that you smoked **regularly** in the past then answer questions below.*	
b. On average, over the entire time you have smoked, how many cigarettes did you smoke per day? NUMBER OF CIGARETTES/DAY:_______	
c. If you stopped smoking tobacco completely, then how long ago did you stop? __________	

Patient ID: ________________

INDIVIDUAL CHARACTERISTICS

SMOKING MARIJUANA

3. Do you currently smoke marijuana?	
☐ Yes	No ☐
If yes, answer questions below	*If no, skip to question 4.*
a. Do you currently smoke marijuana: ☐ Regularly ☐ Irregularly (skip to question 4)	
*If you answered that you smoke **regularly** then answer questions below.*	
b. How old were you when you first started smoking marijuana regularly? __________	
c. On average how much do you smoke per day? NUMBER OF GRAMS PER DAY:________________	
d. On average, *over the entire time* you have smoked marijuana, how much did you smoke per day? NUMBER OF GRAMS/DAY:_____________	

4. Have you smoked marijuana in the past?	
☐ Yes	No ☐
If yes, answer questions below	*If no, skip to question 5.*
d. Did you smoke marijuana: ☐ Regularly in the past ☐ Irregularly in the past (skip to question 5)	
*If you answered that you smoked **regularly** in the past then answer questions below.*	
e. On average, over the entire time you have smoked, how many grams did you smoke per day? NUMBER OF GRAMS/DAY:_______	

INDIVIDUAL CHARACTERISTICS

ALCOHOL CONSUMPTION:

5. The following question is about alcohol consumption. When we use the word drink it means:
    i. One small bottle or can of beer or glass of draft
    ii. One glass of wine or wine cooler
    iii. One drink or cocktail with 1 ½ ounces of liquor

a. How many alcoholic beverages do you usually drink per week?

- ☐ Never drink
- ☐ Only drink on special occasions
- ☐ 1-2 drink(s) per week
- ☐ 3-6 drinks per week
- ☐ 7-14 drinks per week
- ☐ More than 14 drinks per week

b. How often do you have six or more drinks on one occasion?

- ☐ Never
- ☐ Less than monthly
- ☐ Monthly
- ☐ Two to three times per week
- ☐ Four or more times per week